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Editorial

Recent Advances in the Treatment of Cardiac Arrhythmias

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Many important advances have been made in the therapy of cardiac arrhythmias within the last decade. These have resulted from a combination of many factors: (1) improved methods of diagnosis, (2) an increase in our knowledge of the causes, mechanism of production, and precipitating factors tending to induce cardiac arrhythmias, (3) improved information relative to the more scientific use of older antiarrhythmic drugs (e.g., digitalis, quinidine, and Isuprel), and (4) the use of relatively new measures in therapy.

DIAGNOSIS

Proper therapy depends upon (1) the correct diagnosis of the type of arrhythmia, and (2) the alteration in the cardiac function underlying its production. The former may be obtained from the electrocardiogram, but the latter is often difficult to ascertain, even though a complete history, physical examination, and laboratory data have been obtained.

Improved methods of diagnosis have resulted from (1) the greater availability and use of more simplified, relatively inexpensive portable electrocardiographic apparatus, including the new transistor models for use in the wards of the hospital, operating room, and at the patient's home; (2) the more frequent employment of continuous electrocardiographic monitoring during surgery, cardiac catheterization, and infusion of cardiac drugs in bad-risk patients; and (3) the training of interns, residents, and anesthesiologists in the diagnosis of specific arrhythmias, which has resulted in earlier and more definitive therapy. The use of right precordial and esophageal leads and other procedures to determine the auricular mechanism in rapid ectopic rhythms has enabled us to differentiate more definitely between supraventricular and ventricular tachycardia, thereby providing more specific indications for therapy. For example,

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digitalis is often required in large doses to break up a supraventricular tachycardia, whereas it is usually ineffective or contraindicated in the ventricular variety.

AVAILABLE METHODS OF THERAPY

Some of the important advances in the treatment of cardiac arrhythmias are discussed under the methods of therapy mentioned below:

Vagal Stimulation.—Vagal stimulation is efficacious in supraventricular tachycardias, particularly those of auricular or nodal origin. This may be accomplished by mechanical means (carotid or ocular pressure), drugs, or a combination of both. Carotid sinus pressure, properly applied, is often efficacious in terminating the arrhythmia; ocular pressure is not recommended because it carries with it the danger of retinal detachment. The use of emetics (e.g., ipecac) is another method of producing vagal stimulation. Of the parasympathetic drugs, Prostigmin (administered intramuscularly) and digitalis (oral, intramuscular, or intravenous) are probably the safest. Beta methylcholine (Mecholyl) is not recommended because of its frequent untoward effects.

Drugs Which Decrease Excitability.—The most important of the drugs which decrease excitability are quinidine, procaine amide, and potassium salts. These are indicated in the treatment of extrasystoles and paroxysmal tachycardias of auricular and nodal origin, as well as those of ventricular origin.

Quinidine: The use of plasma levels has been a considerable aid in therapy; the therapeutic level usually ranges between 4 and 10 mg. per liter. However, toxic effects may occur at the higher levels. The value, as well as the limitations, of plasma levels in therapy should be considered in the individual patient.

Probably the best criterion of quinidine action consists in the electrocardiographic findings. S-T, T wave, Q-T, and Q-U alterations are usually observed within the therapeutic range; the occurrence of toxic effects in the electrocardiogram consists of a decrease in the auricular beats and a widening of the QRS complexes. If the widening exceeds 0.14 second, further administration should be discontinued. Occasionally, in older patients and in those with severe heart damage, even small doses, 0.2 Gm. (3 grains) four times a day, may produce toxic effects in the form of QRS widening. Repeated electrocardiographic observation in the initial stages of quinidine therapy in this group will detect early toxic effects.

In patients who receive quinidine for long periods it is difficult, with the usual doses administered, to maintain an effective concentration of quinidine during the entire day. Recently, a long-acting quinidine preparation (quinidine gluconate) has been developed which in a dose of about 1.2 Gm. per day (0.4 Gm. three times a day) will maintain a continuous effective level.[1]

Recently, experimental observations have shown that the cardiotoxic effects of quinidine, consisting of widened QRS complexes and hypotension, may be reversed by molar sodium lactate. These observations have been made in the dog and in some human cases.[2]

Procaine amide: Procaine amide is a very effective antiarrhythmic agent and is indicated in extrasystoles and paroxysmal tachycardia of auricular,

nodal, and ventricular origin. It may be administered orally, intramuscularly, or intravenously. The preferred parenteral route is by intramuscular injection, because an effective level is attained within one-half to one hour, and hypotensive effects are relatively minor. If the intravenous route is mandatory in cases of hypotension or shock, it is suggested that the infusion be given in conjunction with vasopressor agents (norepinephrine); the first 500 mg. may be given at a rate of 100 mg. per minute. Thereafter, subsequent injections should be given at a rate of 100 mg. every four minutes, because the maximum effect of a single injection occurs within four minutes. Patients receiving intravenous infusion should be continually monitored.

The use of quinidine or procaine amide is contraindicated in patients subject to Stokes-Adams seizures, even though numerous extrasystoles, ventricular tachycardia, or paroxysms of ventricular fibrillation are present. Doses sufficient to control the extrasystolic arrhythmias may also depress the normal cardiac pacemaker, thus resulting in ventricular fibrillation and/or cardiac arrest. The cardiotoxic effects of procaine amide are similar to those produced by quinidine and can also be reversed by molar sodium lactate.

Drugs Which Increase Excitability.—The drugs which increase excitability include the sympathomimetic group (epinephrine, Isuprel, ephedrine, molar sodium lactate, etc.). They are indicated particularly in the treatment of slow heart rates and periods of cardiac arrest during Stokes-Adams seizures and other states.

Epinephrine: Epinephrine manifests a powerful effect in increasing the rhythmicity of cardiac pacemakers. It will accelerate the slow heart rates and may result in a restoration of cardiac beating in the presence of cardiac arrest. However, its disadvantage is that it tends to stimulate the heart muscle directly, thus producing a sudden increase in cardiac work and increased cardiac irritability, which may precipitate various ectopic rhythms, including ventricular tachycardia, flutter, or fibrillation. The problem consists in the administration of an effective dose at a speed which will be effective in restoring cardiac beating but yet insufficient to produce toxic effects. This point is difficult to determine in the individual patient.

Isuprel: Isuprel is an extremely valuable agent in increasing cardiac rhythmicity. It is effectual in increasing the ventricular rate in complete A-V heart block and restoring cardiac beating in the presence of cardiac arrest. Isuprel has the added advantage of not being so profibrillatory as epinephrine, and it may be administered to patients who have extrasystoles without necessarily producing an increase in ectopic beats. The sympathomimetic drugs (epinephrine, Isuprel, norepinephrine, and others) tend to lose their pressor and pacemaker effects in the presence of acidosis; these properties can be regained by the restoration of a more normal pH, by the administration of molar sodium lactate or some other alkalinizing agent.

Molar sodium lactate: Molar sodium lactate is a powerful agent in increasing cardiac rhythmicity; its principle of action is different from that of sympathomimetic amines. Molar sodium lactate is particularly efficacious in the treatment of slow heart rate due to or associated with hyperpotassemia,[3] in the car-

diac arrest occurring in Stokes-Adams syndrome, in surgery, and in that due to other factors. Molar sodium lactate appears to manifest its effect by one or a combination of the following factors: (1) a decrease in acidosis or production of alkalosis, (2) a possible vagolytic effect, (3) a decrease in serum potassium (which occurs rapidly following the infusion) which tends to increase rhythmicity of the cardiac pacemakers, (4) an effect of the lactate ion. Comparisons with epinephrine have suggested that molar sodium lactate does not tend to cause ventricular fibrillation when used in comparably effective doses and under similar conditions. Because its action is based on a principle different from that of the vagolytic and sympathomimetic drugs, it may supplement these agents and has been effective in conditions where the others were entirely ineffective.

ELECTROLYTE ALTERATIONS

One of the most significant advances in therapy has been the knowledge that the electrolyte alterations observed in disturbances of acid-base balance, involving particularly potassium and, to a lesser degree, sodium and calcium, may precipitate ectopic rhythms. The restoration of normal electrolyte balance will frequently restore normal rhythm.

Potassium.—Alterations in potassium have been studied most extensively. Hypopotassemia results in the production of various types of ectopic rhythms (extrasystoles, auricular tachycardia with and without A-V block, paroxysmal auricular fibrillation, and other arrhythmias). Often its presence may be obscured by the underlying clinical state, e.g., congestive failure, toxic states, gastrointestinal and renal disease. These arrhythmias usually respond poorly to measures other than potassium administration.

The arrhythmias observed with hyperpotassemia include nodal bradycardia, extrasystoles, and a slow idioventricular rhythm. In addition, we have recently noted in a number of patients rapid nodal tachycardias due to hyperpotassemia (rate 140 to 160 per minute). These can be reversed almost immediately by the use of molar sodium lactate.[4]

It should be noted that the cardiac effect of a given concentration of potassium is influenced also by the concentration of other electrolytes, especially sodium and calcium, which are pharmacologic antagonists of potassium.

Indications and methods of administration of potassium: Potassium administration is indicated for arrhythmias associated with hypopotassemia, especially for those associated with digitalis toxicity. It should be noted, however, that potassium is almost equally efficacious for arrhythmias (auricular and ventricular extrasystoles and paroxysmal tachycardias) not associated with hypopotassemia or digitalis toxicity.[5] We prefer the slow intravenous infusion of potassium chloride for the treatment of acute disturbances in rhythm, because evidence of toxicity can be noted immediately, the infusion stopped, and the toxic effects reversed almost immediately by the use of molar sodium lactate or 50 per cent glucose. The oral administration of potassium, while efficacious, may be more dangerous, because the maximum plasma concentration occurs within about one and one-half to two hours, and oral intake is more difficult to monitor electrocardiographically.

Other Electrolytes.—The effects of other individual electrolytes in the production of arrhythmias have not been studied extensively. The effects of magnesium, except for a specific deficiency of this electrolyte, are generally quite similar to those of potassium. The levels of serum sodium and calcium are important because they are pharmacologic antagonists of potassium; a low sodium or calcium would tend to enhance, whereas an increased sodium or calcium would decrease, the potassium effect.

Alterations in acid-base balance are associated with shift in plasma electrolytes and may manifest a profound effect on the production of arrhythmias. In a general way, the tendency is for alkalosis to increase, and acidosis to decrease, cardiac rhythmicity. There are many exceptions to this, and the totality of factors that are operative in a given case are not always easy to elucidate.

A shift in pH may also alter the effects of existing concentration of digitalis, quinidine, procaine amide, and other drugs. For example, it has been shown recently that quinidine acts by preventing the efflux of potassium from the cells to the extracellular phase and the influx of potassium from the extracellular fluid into the cells.[6] The shifts may be altered by changes in pH. The use of solutions to return acid-base balance to normal will often have a salutary effect in reducing an important cause for the production of ectopic rhythms.

IMPROVEMENT IN CARDIAC FUNCTION

Frequently ectopic rhythms are produced by derangements in cardiac function which are associated with various types of myocardial disease and cardiac strain. These may result in the production of anginal or congestive failure. The removal or decrease of this strain by rest, diuretics, and various measures which are directed at the cause, and which improve the underlying clinical state, will have an indirect effect on the abolition of the ectopic rhythms.

Digitalis.—Digitalis, aside from its effect in improving cardiac function, is an important antifibrillatory agent and is indicated in the control of the ventricular rate in auricular fibrillation, conversion of auricular flutter to auricular fibrillation, and in the treatment of auricular and nodal tachycardia. It will often abolish extrasystoles that are associated with congestive failure.

Digitalis toxicity: Digitalis toxicity will produce almost any type of arrhythmia, including auricular and nodal tachycardias (rarely auricular flutter and fibrillation), paroxysmal tachycardia with A-V block, various degrees of A-V heart block, A-V dissociation, and ventricular tachycardia. The treatment consists of: (1) prophylactic measures to prevent toxicity, (2) restoration of normal acid-base and electrolyte balance to normal, (3) use of potassium, and (4) use of quinidine or procaine amide, which may be effective if potassium fails.

Digitalis tolerance tests: A digitalis tolerance test devised by Lown and Levine[7] is based upon the summation of action to the point of toxicity between fractionally administered doses of acetyl strophanthidin and previously administered doses of digitalis. This test has been proved to have definite clinical value but has been found dangerous in many instances.

Another test, devised by Nalbandian and associates,[8] is based on the in-

verse quantitative synergistic relationship between calcium and digitalis to produce electrocardiographic end points. The end point consists in the development of various electrocardiographic signs of digitalis toxicity, e.g., A-V heart block, extrasystoles, etc. These toxic effects can be reversed almost immediately by Versene (Na EDTA). We feel that the disadvantages of this test are as great as those of acetyl strophanthidin.

The Use of Electrical Devices.—Recently, many devices to increase cardiac rhythmicity and to defibrillate the heart have been developed; these have proved to be invaluable in the therapy of various cardiac disorders. The following may be mentioned:

External pacemaker: The pacemaker[9] which may be applied to the intact chest has been successful in the restoration of cardiac beating. Cardiac resuscitation has occurred in patients with cardiac arrest of various etiologies. It is claimed that the artificial external pacemaker acts like a natural intracardiac parasystolic focus, except that it is under complete control. This device is now widely applied and its value in therapy established.

External defibrillator: Episodes of ventricular fibrillation occurring in the Stokes-Adams syndrome and during monitoring in cardiac catheterization have been terminated by the use of an external defibrillator which applies an electric countershock across electrodes on the chest. This procedure is regarded as safe, practical, and rapidly effective.[10,11] If defibrillation should be followed by ventricular standstill, the heart can be stimulated by the artificial cardiac pacemaker.

Countershock: Recently, Zoll and associates[10] have developed a technique whereby the application of a countershock has been successful in terminating a ventricular tachycardia and other types of rapid ectopic rhythms. This procedure has been used in the experimental animal, but, except for an occasional instance, it has not as yet been applied to the human subject.

Pacemaker for use in complete A-V block: Recently, a small pacemaker has been developed (transistor model) which has been efficacious in maintaining adequate beating of the heart for as long as 21 days in the dog and for a similar period in human subjects. A fine silver wire was inserted into the myocardium and the distal end sewn into the skin of the chest. The advantages of such a pacemaker are: (1) The voltage output required is quite small (1.5 to 4.5 volts). (2) It is accompanied by no sensations, contractions of the skeletal muscles, or infection.[12,13] We have been working with similar transistor models, and the results appear to be quite encouraging and to have a wider application than the external pacemakers now available.[14]

Other Procedures.—

Thumping on the precordium: Following cessation of the heart beat during periods of collapse, a vigorous thump over the precordium frequently restores the cardiac beating and obviates the use of other measures to restore the heart beat.

Irritation of the myocardium: Irritation of the heart by the blunt edge of a needle has resulted in restoration of cardiac beating in patients with cardiac arrest and ventricular fibrillation.

Thoracotomy: Cardiac arrest and/or ventricular fibrillation which is not immediately restored to normal beating requires thoracotomy. Cardiac massage and positive pressure respiration should be instituted within 4 minutes after the cessation of cardiac beating. If ventricular fibrillation appears, the heart may be defibrillated by the application of a current to electrodes placed directly over the heart.

Monitoring devices: The use of a monitoring device with a warning signal to detect the occurrence of cardiac arrest in patients with Stokes-Adams seizures, and in those prone to develop episodes of cardiac slowing or cardiac arrest during or following surgical or other procedures, is a valuable aid in treatment. Such patients should be placed in a special ward and the personnel trained in the various methods of restoring the cardiac beat upon notification by the warning signal. The amount of time available to obtain adequate resuscitation with normal brain function is extremely short—only four minutes.

SUMMARY

There have been many developments in the diagnosis and treatment of cardiac arrhythmias in the past decade. These have consisted in the amplification and use of monitoring devices which have been of help in the detection of cardiac arrhythmias and in following the results of therapy. There has been an increase in knowledge relative to the use of previously known antiarrhythmic drugs, and the development of new drugs and therapeutic procedures. Although many arrhythmias are still refractory to present methods of therapy, an increase in our knowledge of their origins and of recent advances in therapy should help to control a larger percentage of these ectopic rhythms.

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Arterial Pressure Pulse Contour and Valsalva Maneuver in Suspected Aortic Stenosis

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In many cases of aortic stenosis the arterial pressure pulse contour is not pathognomonic.[1-3] It was shown in a previous investigation[4] that in cases of aortic stenosis with a normal resting pulse tracing the intra-arterial administration of Priscoline* and subsequent performance of a Valsalva maneuver may elicit the stenotic pattern by propagation of the central pulse contour to the peripheral artery. Gorlin and associates[5] postulated that a pathologic response to the Valsalva maneuver may help in the diagnosis of aortic stenosis, although a normal or intermediate response may occur even in cases of aortic stenosis exhibiting a stenotic pulse pattern.

The aim of this study was to investigate the incidence of normal and stenotic pulse contours as well as the incidence of normal and altered Valsalva responses in cases of suspected aortic stenosis. Furthermore, the effect of Priscoline on the Valsalva response was studied. The alterations in Valsalva response produced by Priscoline were related to the effect of this drug on the pressure pulse contour.

MATERIAL AND METHOD

One hundred and nine patients were included in this study. They were referred by the Cardiac Outpatient Clinic. The majority of them exhibited no cardiac disability, although in some a moderate functional incapacity was present. In each case physical examination revealed a basal systolic murmur, compatible with the diagnosis of aortic stenosis. The electrocardiographic and x-ray findings either were within normal limits or pointed to predominance of the left ventricle. On the basis of these findings the presence of aortic stenosis was suspected. No other cardiovascular abnormalities were detected.

Direct arterial pressure pulse tracings were obtained through an indwelling Cournand needle (No. 18) in the brachial artery. The pressure was recorded on a Sanborn Twin-Viso-Cardiette through a Statham strain-gauge transducer. Continuous pressure tracings were obtained before, during, and after the Valsalva maneuver, and again after intra-arterial administration of 15 mg. of Priscoline, according to the technique described in a previous publication.[4]

The criteria for the aortic stenotic pulse pressure pattern were: prolongation of the crest time, appearance of anacrotic phenomena (anacrotic break, notch, or vibrations), and normal or

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*Priscoline = Tolazoline hydrochloride = 2-benzyl-4,5-imidazoline hydrochloride.

small pulse pressure.[6] The pressure response to the Valsalva maneuver was divided into three types[5,7]: (1) normal response—indicating a marked decrease of systolic pressure with diminution of pulse pressure during the straining period and appearance of overshoot in the poststraining phase; (2) intermediate response—minimal or delayed decrease of systolic pressure and/or pulse pressure, or absence of normal overshoot; and (3) pathologic response—increased systolic pressure during straining period and absence of overshoot.

RESULTS

The results have been divided into 2 groups, according to the resting pulse contour.

1. *Suspected Aortic Stenosis With Normal Resting Pulse Contour.*—This group consisted of 97 patients. Forty patients showed a normal Valsalva response. In 38 of these the intra-arterial administration of Priscoline did not cause significant changes in the pulse contour or in the Valsalva response (Fig. 1). Only 2 patients exhibited a stenotic pulse pattern in the presence of a normal Valsalva response.

Forty-three patients exhibited an intermediate Valsalva response. In 28 of these the administration of Priscoline did not change the normal resting pulse contour, and the response to the Valsalva maneuver was converted to normal in 20 patients (Fig. 2) and remained intermediate in 8. In the remaining 15 patients Priscoline provoked a stenotic pulse pattern, and the Valsalva response remained intermediate in 11 (Fig. 3) and became pathologic in 2. In 2 patients the Valsalva response changed toward normal.

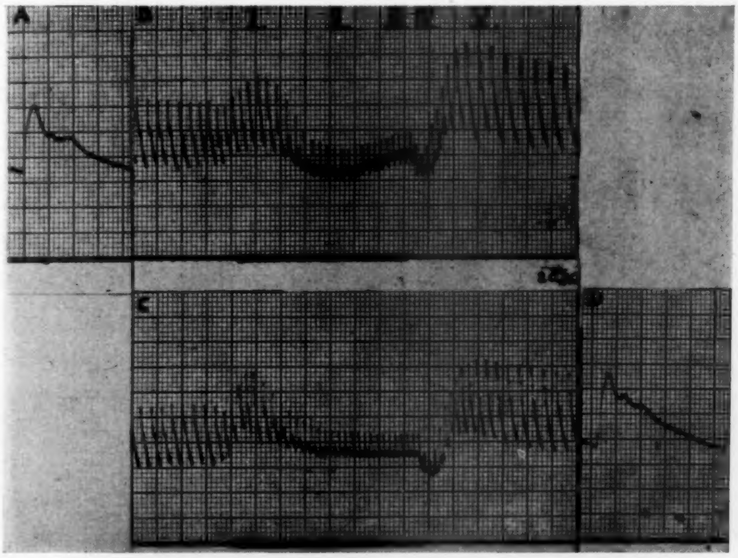

Fig. 1.—*A*, Normal resting pulse contour. *B*, Normal Valsalva response, characterized by initial pressure rise (*I*), marked decrease of systolic and pulse pressures (*II*), secondary pressure rise (*III*), sudden drop of pressure at release of expiratory effort (*IV*), and overshoot (*V*). *C*, Post-Priscoline Valsalva response differing from the previous one by absence of secondary pressure rise and by smaller overshoot. *D*, Following Priscoline the pulse contour in the poststraining phase is similar to the resting contour.

In this and all subsequent figures the heavy line at the bottom of the record indicates straining period. Time is in seconds.

Fourteen patients with normal resting pulse contour exhibited a pathologic Valsalva response. In 9 of these the administration of Priscoline elicited the appearance of a stenotic pulse pattern, without affecting the pathologic Valsalva

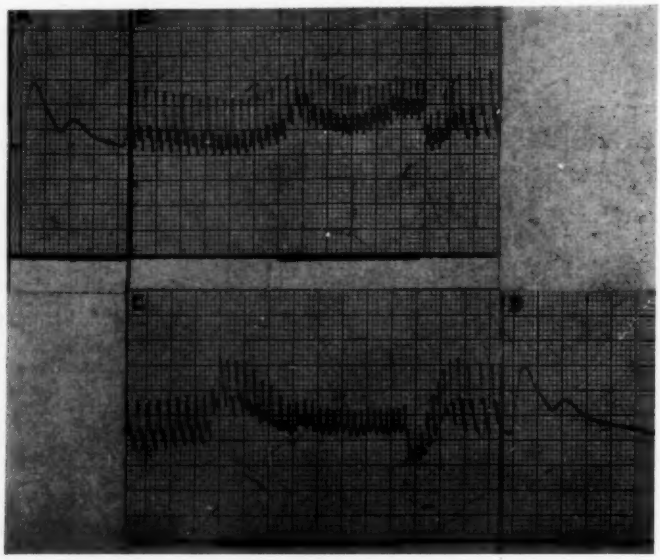

Fig. 2.—*A*, Normal resting pulse contour. *B*, Intermediate Valsalva response, characterized by slight decrease of systolic and pulse pressures and by slight overshoot. *C*, Valsalva response changed to normal following Priscoline. *D*, Post-Priscoline pulse contour similar to the resting one.

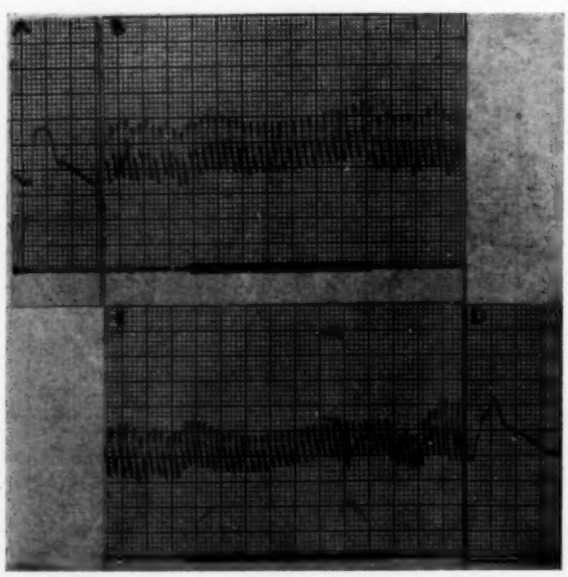

Fig. 3.—*A*, Normal resting pulse contour. *B*, Intermediate Valsalva response indicated by minimal decrease of systolic and pulse pressures and absence of overshoot. *C*, Administration of Priscoline did not cause significant change in the intermediate Valsalva response. *D*, After Priscoline the pulse contour in the poststraining phase resembles that of aortic stenosis.

response (Fig. 4). In 5 patients there was no change in the pulse contour following administration of Priscoline. In 4 of these the Valsalva response shifted toward either normal or intermediate; in the fifth patient the Valsalva response was unaltered.

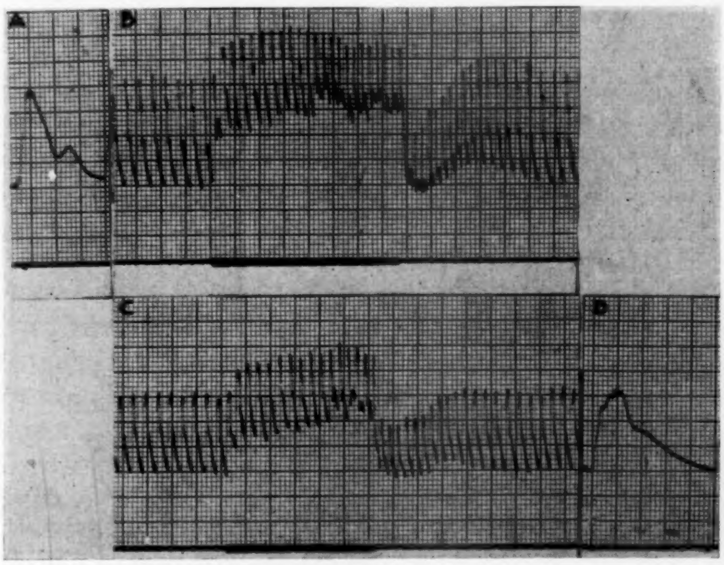

Fig. 4.—*A*, Normal resting pulse contour. *B*, The sustained pressure rise during the Valsalva maneuver indicates pathologic response. *C*, The post-Priscoline Valsalva response does not differ from the previous one. *D*, Priscoline provoked the appearance of stenotic pulse contour in the poststraining phase.

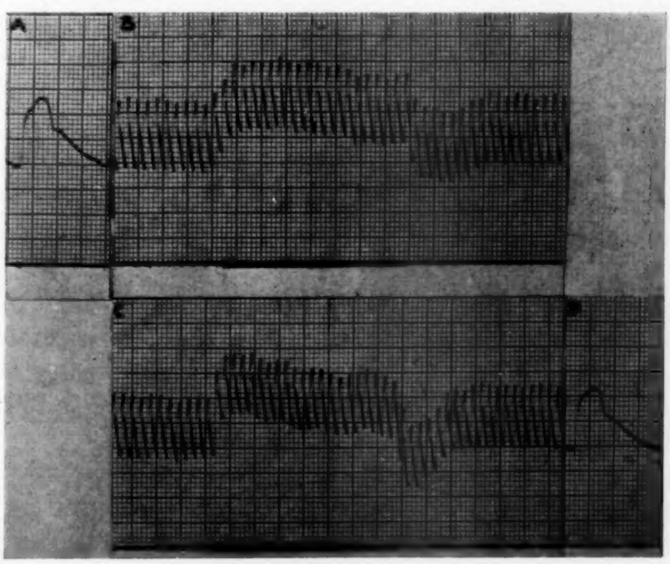

Fig. 5.—*A*, Stenotic resting pulse contour. *B*, Pathologic Valsalva response. *C*, The post-Priscoline Valsalva response does not differ from the previous one. *D*, The pulse contour is not altered by Priscoline.

2. *Suspected Aortic Stenosis With Stenotic Resting Pulse Contour.*—Twelve patients had a stenotic pulse contour at rest. The Valsalva maneuver was pathologic in 9 of them, intermediate in 2, and normal in 1. Priscoline either had no effect on the pulse contour or exaggerated the signs of aortic stenosis, and the response to the Valsalva maneuver was unaltered (Fig. 5).

COMMENT

In normal subjects during the straining phase of the Valsalva maneuver the high intrathoracic pressure diminishes the filling pressure and the valve pressure gradient in the left heart.[5,8] The result is a reduction in valve flow and stroke work, causing a marked fall in the arterial mean pressure and pulse pressure. Gorlin and associates[5] have shown that in the presence of a diminished valve area, and/or in the presence of a high filling pressure, this pressure-flow relationship is altered; consequently, during the straining phase of the Valsalva maneuver the decrease in filling pressure and in the valve pressure gradient reduce the flow to a much smaller extent than in normal subjects. This is reflected either by a slight fall, no change, or even a rise in the peripheral arterial pressure. Since the decrease of flow is determined by the size of the aortic valve area and by the state of ventricular function, one would logically expect that in various degrees of aortic stenosis, pathologic, intermediate, or even normal Valsalva responses would be encountered.

Gorlin and associates[5] reported pathologic responses in patients with tight aortic stenosis, but intermediate or normal responses even in patients with a pathognomonic pulse pattern. Other investigators found normal Valsalva responses in the presence of aortic stenosis.[9-11] Pathologic responses have been described also in heart failure[12,13] and in mitral stenosis.[11,14,15] Twenty-three pathologic responses were observed in our patients in whom aortic stenosis was the suspected diagnosis. Since these patients showed no signs of heart failure or of mitral stenosis, the pathologic response could be explained only by aortic valve obstruction.

The pressure pulse contour is of help in diagnosing aortic stenosis when it has the pathognomonic pattern; however, it may remain normal in many cases. Only 12 of our patients showed a stenotic pulse contour. Since the appearance of a pathologic Valsalva response and the presence of a stenotic pulse pattern both result from a reduced valve area and impaired ventricular function, an attempt was made in this study to correlate these phenomena. Our data show that the stenotic pulse pattern is usually accompanied by a pathologic Valsalva response, and that the normal pulse contour is generally associated with a normal or intermediate Valsalva response. Fourteen patients, however, exhibited a pathologic response in the presence of a normal pulse contour.

It was reported in an earlier publication[4] that in cases of aortic stenosis with normal resting pulse contour, the intra-arterial administration of Priscoline with the subsequent performance of a Valsalva maneuver may lead to the appearance of a central-like, stenotic pulse contour. This alteration results from the abolishment of peripheral reflected waves in the presence of impaired ventricular function, and also from the additional burden on the left ventricle in the poststraining

phase of the Valsalva maneuver. The appearance of a stenotic pulse pattern after this procedure, in 9 out of 14 patients who had an abnormal Valsalva response and a normal pulse contour at rest, served as further support to the diagnosis of aortic stenosis.

It is of importance to determine whether the intermediate Valsalva response signifies a normal or a pathologic reaction. It has been stated that the intermediate response has pathologic significance if it is not altered by changing posture of the patient,[5] mild exercise,[7] or the administration of ganglionic blocking agents.[16] In our study, Priscoline, a sympathicolytic, adrenolytic agent, was used to evaluate the intermediate response. The administration of this drug in patients with intermediate Valsalva response either caused a change toward normal or had no appreciable effect, as has been found by Stucki and associates[16] using tetraethylammonium chloride. In patients exhibiting a normal Valsalva response the administration of Priscoline abolished the secondary pressure rise during the straining phase, and diminished the overshoot; these observations were similar to those made following the administration of ganglionic blocking agents.[17,18] The pathologic Valsalva response was not altered by Priscoline in those of our patients who revealed a stenotic pulse pattern prior to or following Priscoline. It has already been reported that the pathologic Valsalva response is not modified by ganglionic blocking agents.[16] It is noteworthy that in 4 out of 5 pathologic Valsalva responses in patients with normal pulse contours, even after Priscoline, a partial or complete normalization of the Valsalva response was achieved. We cannot offer any satisfactory explanation for this observation; it is possible that we dealt with the phenomenon of false positive Valsalva response in these cases, which is supposed to be a technical error.[5]

A fairly good relation was found between the change in pressure pulse contour following Priscoline and the effect of this drug on the intermediate Valsalva response. In the majority of patients with a normal pulse contour, even after Priscoline, the intermediate Valsalva response changed to normal. On the other hand, in those patients in whom Priscoline provoked a stenotic pulse pattern, the intermediate response remained unaltered. This may indicate that the abnormal Valsalva response was due to the impairment in the performance of the left ventricle.

We conclude, therefore, that the majority of patients with suspected aortic stenosis exhibit a normal pulse contour and a normal Valsalva response, whereas a stenotic pulse contour is accompanied by a pathologic Valsalva response. In doubtful cases Priscoline has been of diagnostic help either by changing the pulse contour or by altering the Valsalva response.

SUMMARY

In 109 patients with suspected aortic stenosis a direct arterial pressure pulse tracing and the response to the Valsalva maneuver were recorded prior to and following intra-arterial administration of Priscoline.

The majority of the patients revealed a normal pulse contour which was accompanied by a normal, intermediate, or pathologic Valsalva response. Stenotic pulse contour was usually associated with pathologic Valsalva response.

Administration of Priscoline diminished both the secondary pressure rise during the straining phase and the overshoot in patients who exhibited normal Valsalva response. Pathologic Valsalva response was not altered by the drug. In patients with intermediate Valsalva response Priscoline either modified the response toward normal or had no appreciable effect.

In the majority of the patients with a normal resting pulse contour and an intermediate Valsalva response, Priscoline either provoked a stenotic pulse contour and the Valsalva response remained unaltered, or the pulse contour remained normal and the Valsalva response changed to normal.

The recording of pulse contour and Valsalva response before and after Priscoline is thought to be of diagnostic help in doubtful cases of aortic stenosis.

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Early Electrocardiographic Changes Produced by Ascending to High Altitudes

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In a previous study 10 subjects were taken from sea level to high altitudes; where observations were carried out, first, after 1 month of residence and, then, periodically for a whole year. During the progressive acclimatization, changes in the electrocardiogram were observed which resembled, at least in part, the electrocardiographic characteristics of the native residents of high altitudes.[1] Nevertheless, the early electrocardiographic response to anoxic anoxia determined by the ascent to high altitudes was not studied. On the other hand, however, recent experimental observations demonstrate that early right ventricular hypertrophy can be produced in guinea pigs exposed for several weeks to simulated high altitudes.[2] Therefore, we believed that new investigations should be performed on man in order to study the early electrocardiographic changes produced by the ascent to high altitudes.

MATERIAL AND METHODS

Thirteen normal men between the ages of 17 and 21 years were studied. In Lima, at sea level, an electrocardiogram was recorded. Afterward the subjects were taken by motorcar to Morococha, at an altitude of 4,540 meters (14,900 feet); the ascent took nearly 4 hours. In 5 subjects electrocardiographic observations were made immediately after their arrival at high altitudes; in the other 8, studies were made after 12 hours, and again on the fourth, eighth, twelfth, and sixteenth days, with prolonged observation up to 4 weeks in 3 subjects of this group. Finally, these 8 subjects were taken back to sea level where new observations were made at the time of their arrival and on the fourth, eighth and sixteenth days thereafter.

All the tracings were obtained under basal conditions, employing a Sanborn Viso-Cardiette, Model 52. Standard leads, augmented unipolar limb leads, precordial leads, and additional right and high thoracic leads were taken. For vectorial determinations a model described in a previous work was used.[3] In this model the sagittal plane is seen from the left and the horizontal plane from above, the latter being divided into two areas, one anterior positive, and the other posterior negative; the left posterior quadrant is between 0° and −90°, and the right posterior quadrant is between −90° and ±180°.

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RESULTS

Heart Rate.—No significant variation of the heart rate was observed immediately after arrival at high altitude. Twelve hours later the heart rate increased, the highest values being noted between 4 and 8 days of residence at the altitude. Later, the heart rate decreased, and when the subjects returned to sea level, values similar to those of the initial control were obtained after 4 to 8 days (Table I and Fig. 1).

TABLE I. OBSERVATIONS ON THE HEART RATE (BEATS PER MINUTE)

SUBJECTS		1	2	3	4	5	6	7	8
Lima		60	70	67	59	73	72	57	60
Morococha	12 hours	84	80	95	90	93	100	60	100
	4 days	100	90	80	85	95	95	72	90
	8 days	107	90	90	105	79	80	82	88
	12 days	91	90	95	80	87	81	75	75
	16 days	71	75	83	91	88	80	65	70
Lima	8 days	65	70	67	55	60	62	75	70

TABLE II. CHANGES OF ÂP VECTOR

SUBJECTS	1	2	3	4	5	6	7	8
Lima	0°	+75°	+55°	0°	+60°	0°	+30°	+45°
Morococha (16 days)	+65°	+75°	+75°	+65°	+60°	+65°	+75°	+55°
Lima (8 days)	−5°	+75°	+55°	0°	+60°	+60°	+75°	+50°

TABLE III. CHANGES OF QRS COMPLEX

SUBJECTS	SÂQRS FRONTAL PROJECTION			SÂQRS HORIZONTAL PROJECTION			TRANSITIONAL ZONE		
	L	M	L	L	M	L	L	M	L
1	+80°	+80°	+80°	−70°	−70°	−70°	V_3–V_4	V_4	V_3–V_4
2	+45°	+55°	+50°	−20°	−30°	−30°	V_2–V_3	V_3	V_2–V_3
3	+60°	+70°	+65°	−40°	−70°	−55°	V_3	V_3–V_4	V_3
4	−5°	−40°	−5°	−40°	−65°	−60°	V_4–V_5	V_6	V_5
5	+50°	+55°	+50°	−45°	−55°	−45°	V_3–V_4	V_4–V_5	V_3–V_4
6	+70°	+85°	+85°	−60°	−85°	−85°	V_3–V_4	V_4–V_5	V_3–V_4
7	+65°	+70°	+80°	−60°	−60°	−70°	V_3–V_4	V_3–V_4	V_3–V_4
8	?	?	?	?	?	?	$V_{4R} \rightarrow V_3$	$V_{4R} \rightarrow V_5$	$V_{4R} \rightarrow V_4$

L = Lima. The results corresponding to the return from high altitudes were obtained 8 days after return.

M = Morococha. The data correspond to the observations made on the sixteenth day of residence in this place.

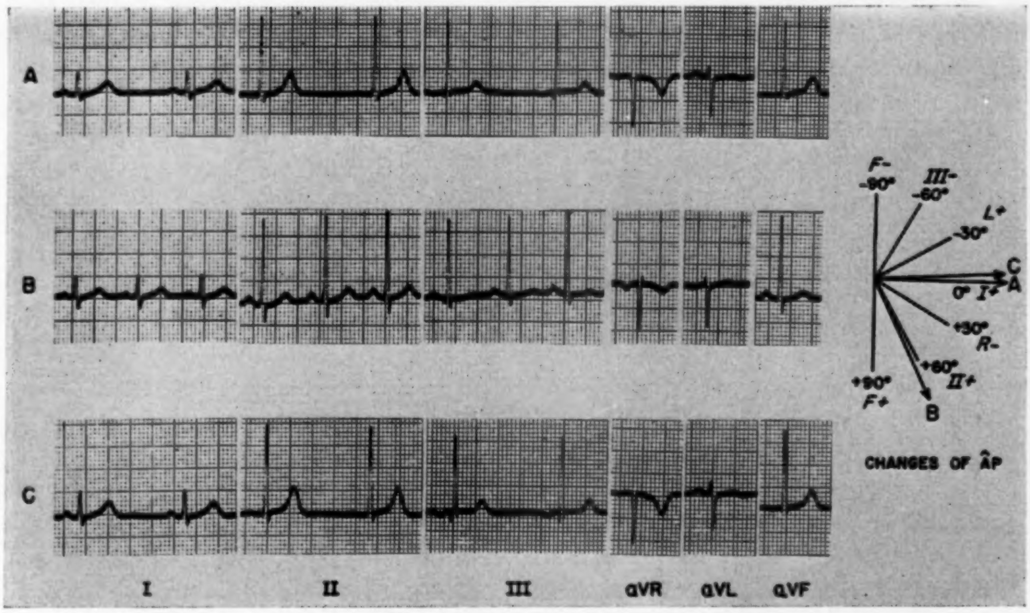

Fig. 1.—Subject 1. *A*, Electrocardiogram obtained in Lima, at sea level. *B*, ECG on the eighth day of residence in Morococha (at an altitude of 14,900 feet). *C*, ECG 8 days after return to sea level. Variations in the heart rate and changes of the ÂP vector can be observed.

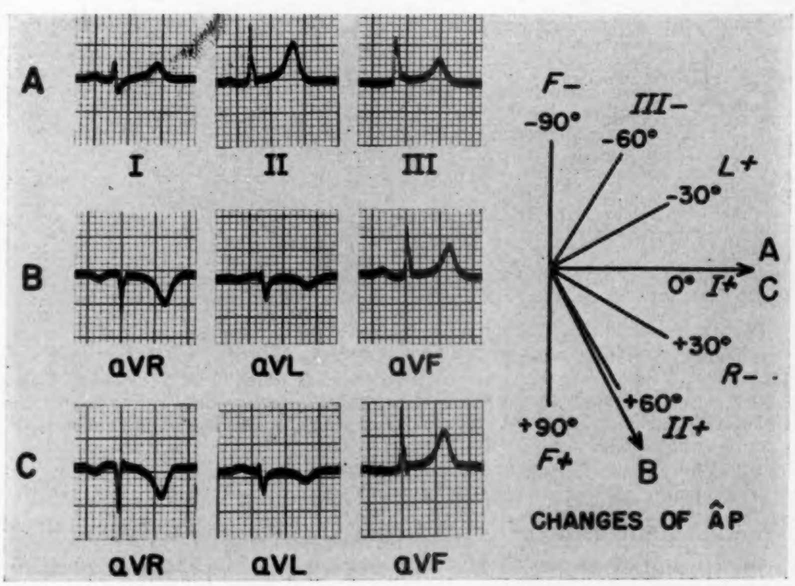

Fig. 2.—Subject 6. *A*, The ÂP vector points toward 0° on the eighth day of residence in Morococha. *B*, A moment later the unipolar limb leads show the ÂP vector placed at +65°. *C*, Four days later, with the subject still in Morococha, the ÂP vector has returned to 0°.

P-R, QRS, and Q-T Intervals.—Slight variations of P-R and Q-T intervals were related to the changes observed in the heart rate. No significant changes of the QRS interval were found.

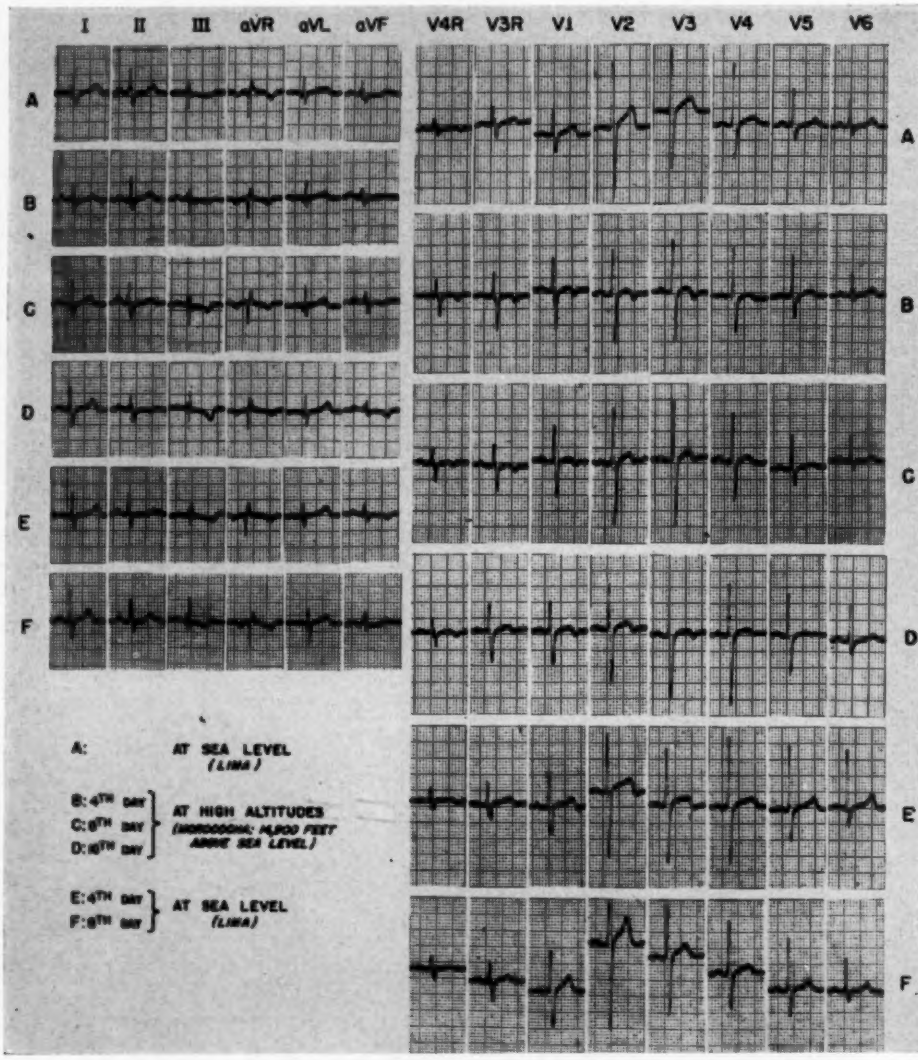

Fig. 3.—Subject 8. On the sixteenth day of residence in Morococha (*D*) left and backward $\hat{S}\hat{A}T$ deviation can be noted. The T wave is negative from Lead V_{4R} up to Lead V_4; the RS-T segment shows an elevation and upward convexity in the same leads, and the transitional zone of QRS has shifted toward the left precordial leads. All these changes disappeared when the subject returned to sea level (*E* and *F*).

P Wave.—No changes occurred immediately after the arrival at high altitude. Afterward, positional changes of the $\hat{A}P$ vector (Table II) and modifications of the P-wave direction in Leads III, aV_F, and sometimes in Leads II and aV_L, were observed in some subjects. These changes were unstable, the variations occurring from one day to the next and even during the same observation (Fig. 2).

When the subjects returned to sea level, the ÂP vector and the direction of the P wave recovered their original characteristics; this occurred after 1 to 2 weeks.

QRS Complex.—No variations were observed immediately after the subjects arrived at high altitude. Later, the following changes were observed in most cases: (1) The transitional zone shifted toward the left precordial leads (Table III). (2) The SÂQRS vector shifted slightly to the right and backward.* (3)

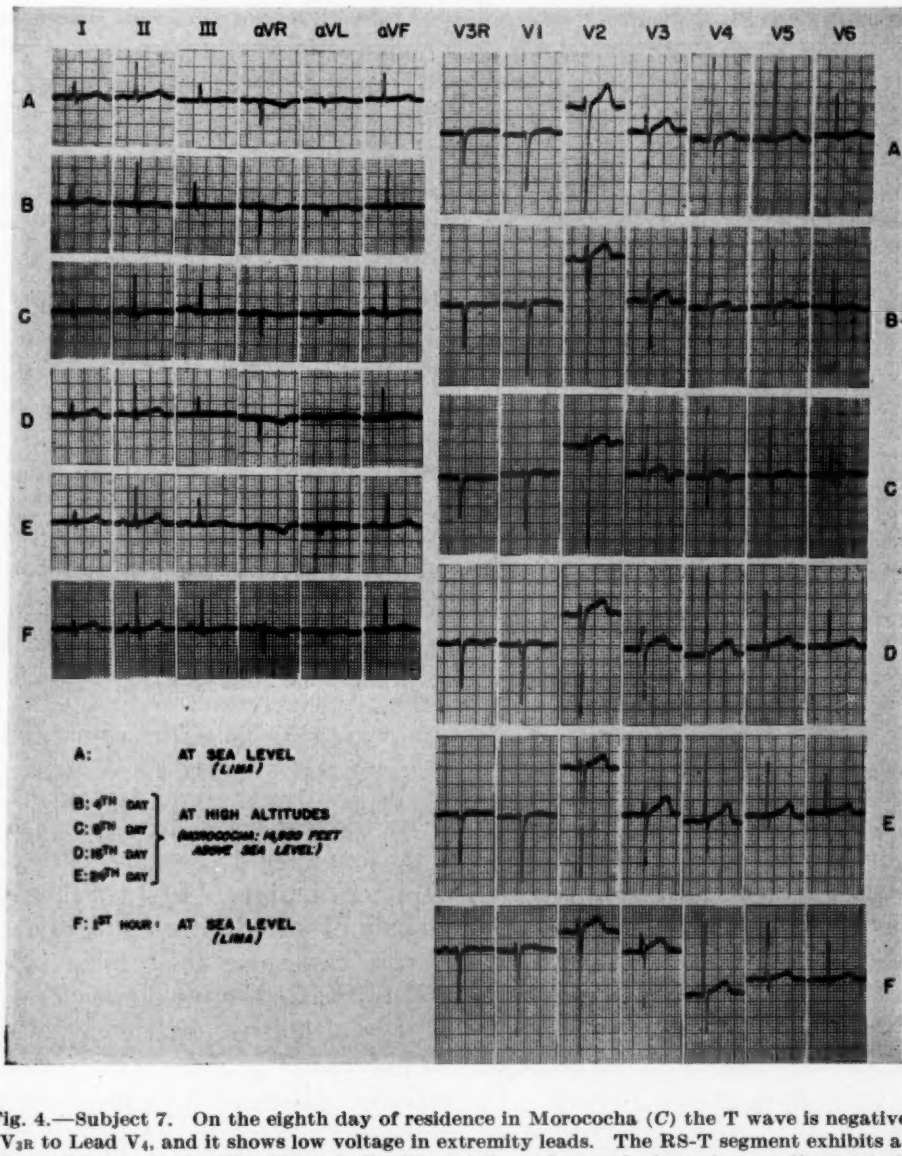

Fig. 4.—Subject 7. On the eighth day of residence in Morococha (*C*) the T wave is negative from Lead V_{3R} to Lead V_4, and it shows low voltage in extremity leads. The RS-T segment exhibits a slight elevation and upward convexity in Leads V_2, V_3, and V_4. Afterward, these changes disappeared while the subject was still in Morococha (*D* and *E*). Variations of the ÂP vector and slight changes of the QRS complex can be observed also.

*Only in one subject (Case 4) was left ÂQRS deviation observed: −5° at sea level and −40° at high altitudes. It is well known that when the ÂQRS vector is located between 0° and −90°, the backward SÂQRS deviation determines left ÂQRS shift on the frontal plane.

The S wave increased its voltage slightly in Leads I and aV_L and in the left precordial leads. (4) The R wave increased its voltage slightly in Leads III and aV_F (Figs. 3 and 4). These changes disappeared 1 to 2 weeks after the subjects returned to sea level.

TABLE IV. CHANGES IN THE HORIZONTAL PROJECTION OF SÂT

SUBJECTS	1	2	3	4	5	6	7*	8
Lima	+20°	+60°	+55°	+40°	+50°	+55°	+35°	+45°
Morococha (16 days)	+45°	+60°	+55°	+25°	+30°	+20°	+10°	−60°
Lima (16 days)	+30°	+60°	+55°	+40°	+55°	+45°	+25°	+45°

*In this subject the greatest backward SÂT deviation (−60°, and negative T wave up to Lead V_4) was observed on the eighth day of residence at Morococha. The ventricular repolarization process became normal during the following 2 weeks of residence in this place.

RS-T Segment and T Wave.—Immediate changes after arrival at high altitudes were not noted. Afterward, in most cases the T wave showed an abnormal contour in the right precordial leads. Some few days later the T wave became negative and the RS-T segment showed a slight elevation and upward convexity in the same leads (Figs. 3 and 4). The forward SÂT orientation decreased, not varying its frontal projection* (Table IV). When the SÂT deviation was slight, the T wave was negative in Leads V_{4R} and V_{3R} and sometimes in Lead V_1. On the other hand, when the SÂT vector shifted to a backward position, negative T waves were observed in the right and medial precordial leads up to Lead V_4 (Figs. 3 and 4). In only one case was regression of the changes observed in the last 2 weeks of residence at high altitudes (Fig. 4). When the subjects returned to sea level the ventricular repolarization process became normal again in all cases in the course of 1 to 2 weeks.

DISCUSSION

Heart Rate.—A rise in the heart rate was the first circulatory response produced by the ascent to high altitude. After the first week the heart rate decreased, but figures similar to those at sea level were not obtained. In a previous work an important decline in the heart rate was only observed after 30 to 60 days of residence at high altitudes, with bradycardia and sinus arrhythmia in some cases.[1] The decline in the heart rate is probably related to the preponderance of the vagal tone[4] and to the development of more definitive mechanisms of adaptation, cardiopulmonary[5] and hematic[6-8] in nature.

Auricular Activation Process.—The variations observed in the mean direction of the auricular activation process are apparently related to a wandering pacemaker in the sinoatrial node, or to synchronous activity, in some periods, of the sinus node and the sinocoronary node.[9] The wandering pacemaker is probably determined by the modifications of the vagal tone.

*Only in Case 8, the subject who showed the greatest backward SÂT deviation, was moderate deviation on the frontal plane observed: +15° at sea level and −30° at high altitudes.

Ventricular Activation Process.—In a previous investigation important changes of the QRS complex were observed after 1 year of residence at high altitudes, and these changes were ascribed to two factors: (1) variations in the cardiac position, and (2) a moderate development of right ventricular hypertrophy, the latter being a consequence of pulmonary hypertension.[1] In the native residents of high altitudes the QRS complex shows signs of right ventricular hypertrophy,[10] and in the same subjects pulmonary hypertension has been proved[5] and right ventricular hypertrophy verified anatomically.[11] When these subjects are brought to sea level the QRS changes regress slowly,[12] as occurs in some heart diseases after surgical treatment. In the present investigation the QRS changes are early and slight, and they promptly disappear when the subjects return to sea level. Therefore, it is probable that these changes are fundamentally related to variations in the cardiac position: clockwise rotation around the long axis of the heart with backward rotation of the apex. This change of the cardiac position would be determined in part by the hyperventilation observed at high altitudes,[13] and in part by the subacute overloading of the right ventricle as a consequence of the modifications of the pulmonary circulation in an environment of anoxic anoxia.[5,14-17] The short time of residence at high altitudes is insufficient for determination in these subjects of the development of an incipient right ventricular hypertrophy. Nevertheless, on the basis of recent experimental data,[2] this possibility cannot be discounted.

Ventricular Recovery Process.—The $\hat{\text{S}}\text{T}$ deviation to the left, backward, and downward (upward in only one case), and the negative T waves in the right precordial leads, suggest the possibility of right ventricular ischemia,[12] which would be related to subacute overloading of the right ventricle produced by the new conditions of the pulmonary circulation as a result of the anoxic anoxia.[5,14-17] The changes in the T wave can be observed from the first days of residence at high altitude, and these changes are similar to those occurring in the residents when they lose their adaptation.[10] Therefore, it is probable that the changes observed in the present investigation indicate delayed or impaired adaptation to the high altitudes. The duration of these changes is quite variable: the T-wave changes regress in less than a month in some subjects, while in others the changes persist after 1 year of residence.[1] This variable behavior would depend on a differing capacity for adaptation to the life at high altitudes.

SUMMARY

1. Electrocardiographic observations were made in subjects taken from sea level to high altitudes, where they remained from 16 to 30 days. The first changes were observed a few hours after the arrival at high altitude, and the modifications were evident some days later. The changes disappeared 1 to 2 weeks after the subjects returned to sea level.

2. The following changes were observed: (a) variations of the $\hat{\text{A}}\text{P}$ vector, which are probably related to wandering pacemaker in the sinus node; (b) changes of the QRS complex, which are explained by variations in the cardiac position; and (c) modifications of the ventricular recovery process, which are prob-

ably related to subacute overloading of the right ventricle and to right ventricular ischemia, as a consequence of the modifications of the pulmonary circulation in an environment of anoxic anoxia.

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Arrhythmias and Vector Electrocardiographic Analysis of Complete Bundle Branch Block in Chagas' Disease: A Study of 103 Autopsied Cases

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In 1909, Carlos Chagas discovered that the cause of the disease which now bears his name is the *Trypanosoma cruzi*, and that it is transmitted by hematophagus *Triatomidae*. The disease begins as an acute and generalized condition which frequently involves the myocardium. The disease may even cause death, particularly in children.[5-8] In its chronic phases, Chagas' disease causes a predominant interstitial myocarditis with dissociation and degeneration of the myofibrils. The evolution of chagasic myocarditis is characterized by successive flare-ups of the disease. We can often find, in the same microscopic slide, distinct evolutionary phases of the myocarditis, and sometimes it is possible to see the nests of Leishmania between or inside the myofibrils.[7-9] The disease frequently presents the most variable arrhythmias,[4-21] and these often cause the patient's death before any hemodynamic evidence is discernible.[4-6]

MATERIAL AND METHOD

One hundred and twenty-four electrocardiograms from 103 patients (82 males and 21 females, aged 7 to 60 years) who were suffering from chronic chagasic cardiopathy were studied.

The diagnosis was based on clinical and laboratory data and was confirmed in all cases at autopsy. In 5 instances additional lesions were found which will be referred to in the electrocardiographic study.

Vector electrocardiographic analysis[22,23] of a tracing from each of 66 patients was made (Fig. 1). In the other tracings the analysis was not considered because of complete atrioventricular (A-V) block, complex arrhythmias, digitalis effect, or technical conditions which would give erroneous results.

Forty electrocardiograms showed complete bundle branch block, of which 29 were right bundle branch block and 11 were left bundle branch block. From 26 remaining instances, 11 showed incomplete left bundle branch block, and in 15 the ventricular conduction was normal.

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RESULTS

The analysis of the rhythm is presented in Table I.

In those 5 instances with additional lesions the following associations were found: auricular fibrillation plus coronary atheroma (1 case); complete A-V block plus syphilitic aortic valve lesion (1 case); right bundle branch block plus aortic and coronary atheroma (1 case); and left bundle branch block plus coronary atheroma and syphilis of the aorta (2 cases).

TABLE I

ECG FINDING	NUMBER OF PATIENTS	PER CENT OF TOTAL ECGS
Normal electrocardiogram	2	1.61
Sinus tachycardia	19	15.32
Sinus bradycardia	2	1.61
Extrasystoles	94	75.80
auricular	*4*	3.22
nodal	*5*	4.03
supraventricular	*1*	0.80
ventricular, unifocal	*27* } *84*	21.77 } 67.73
ventricular, multifocal	*57*	45.96
short-run paroxysmal tachycardia	5	4.03
bigeminy	5	4.03
Nodal escape	1	0.80
Sinus arrest	2	1.61
Paroxysmal auricular tachycardia	2	1.61
Paroxysmal ventricular tachycardia	2	1.61
Auricular flutter	3	2.41
Auricular fibrillation	7	5.62
Wandering pacemaker	6	4.82
Chaotic heart action	2	1.61
Interference dissociation	2	1.61
Atrioventricular block	45	36.29
A-V block with prolonged P-R interval	*20*	16.12
A-V block, Mobitz type	*2*	1.61
A-V block, complete	*23*	18.54
Bundle branch block	76	61.29

Type of Block	*Number of Patients*	*Per Cent of Total ECGs (124)*	*Per Cent of Total BBB (76)*
Right BBB	39	31.45	51.31
complete	*37*	29.83	48.68
incomplete	*2*	1.61	2.65
Left BBB	29	23.38	38.15
complete	*17*	13.70	22.36
incomplete	*12*	9.67	15.78
Bilateral "focal" block	8	6.45	10.51

DISCUSSION

Normal electrocardiograms were found in only 2 patients.

Bradycardia was observed with a certain frequency, but sinus bradycardia was registered in only 2 patients.

Extrasystoles were the most frequent type of arrhythmia (75.80 per cent); in most cases they were ventricular and multifocal. In some instances the extrasystoles were so numerous that it was difficult to identify the fundamental ventricular complexes, the tracings showing aspects of chaotic heart action.

Auricular fibrillation was present in 7 patients; thus, chagasic myocarditis is one of the conditions in which this type of arrhythmia may appear. It is interesting that all cases of fibrillation had multifocal ventricular extrasystoles also. Four of these cases were associated with complete right bundle branch block, and one with complete left bundle branch block.

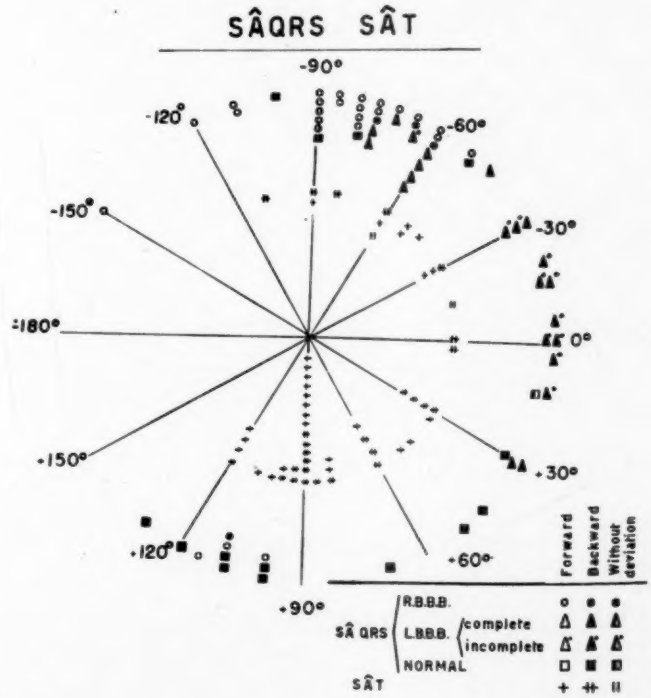

Fig. 1.—The spatial direction of the ventricular activation and repolarization processes in 66 patients with Chagas' disease (29 with complete right BBB and 22 with left BBB).

The A-V blocks occurred rather frequently (36.29 per cent), and in 23 instances (18.54 per cent) there was a complete A-V block. Carlos Chagas[7,8] called attention to the great frequency of this type of block, which he held to be responsible for the bradycardia, dizzy spells, loss of consciousness, and convulsions presented by many of these patients.

In 23 patients with more than one electrocardiogram we observed that the arrhythmia could change from one type to another within rather short intervals. In one patient showing a prolonged P-R interval, the arrhythmia changed to

complete A-V block, and a certain time later it reverted to a prolonged P-R interval. In another patient we were able to observe a complete right bundle branch block changing to focal block and vice versa, within 15 days.

A high incidence of bundle branch block was found (61.29 per cent). The same finding has been reported by all the authors who have studied chagasic cardiopathy.[7-15,17-21,24-29] In accordance with other investigators, we also observed a greater incidence of right bundle branch block. The majority of authors[10-19,25,26,29] are of the opinion that left bundle branch block is a rare occurrence in chagasic myocarditis. In our series of patients, however, this type of block was rather frequent, being observed 29 times; 17 were complete and 12 incomplete.

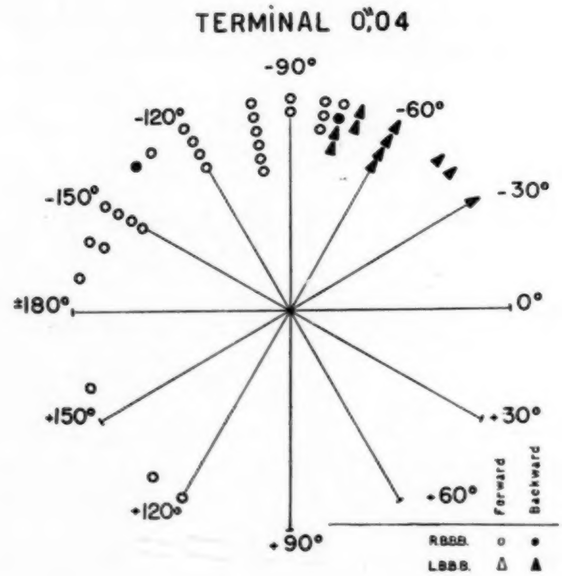

Fig. 2.—The spatial orientation of the terminal vectors of the ventricular activation process in 40 patients with Chagas' disease and complete BBB.

It is interesting to point out that the age of our patients with complete right bundle branch block was between 14 and 58 years (average 33.5 years), and 21 subjects were under 40 years.

The age of the patients with complete left bundle branch block was between 18 and 60 years, with a mean of 33.5 years. It is remarkable that the ages of 5 of these patients were 18, 20, 20, 22, and 23 years, which shows that concomitant atherosclerosis or other disease could not be held responsible for the appearance of this type of block. This lack of association was confirmed by autopsy.

It is possible that the relative discrepancies of the frequency and the types of arrhythmias between our results and those of other authors[10,11,13-21,24-29] can be explained by the fact that our material was obtained in more advanced stages of the disease.

Vectorial Analysis.—In regard to the group with complete right bundle branch block the spatial orientation of the ventricular activation process was

distributed in the majority of the cases in a peculiar and characteristic manner between −60° and −90°, being directed anteriorly in all but 4 cases (Fig. 1).

The final QRS vectors were found more frequently between −100° and −150°, which is also different from the positions usually observed in right bundle branch block[22] (Fig. 2).

SÂT showed a greater opposition to SÂQRS than to the terminal 0.04 vectors (Fig. 1).

This spatial distribution is of great interest in the diagnosis of chagasic myocarditis in patients under 40 years of age, particularly if there is another associated arrhythmia (Fig. 3).

It seems to us that the upward, leftward,[31] and anterior direction of SÂQRS in these cases of right bundle branch block can be related to the findings at necroscopy of diffuse lesions with biventricular dilatation and hypertrophy (especially of the left ventricle), associated with areas of fibrosis, mainly in the apical region. These anatomic data were found also by other authors.[30]

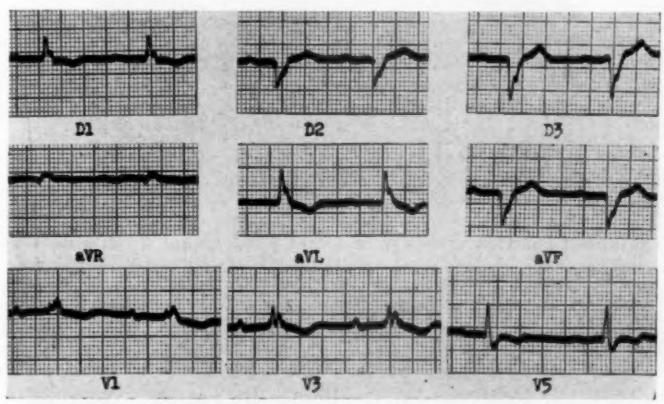

Fig. 3.—Electrocardiogram of a 39-year-old man with chagasic myocardiopathy, proved at autopsy. A complete right BBB with leftward and upward deviation of ÂQRS and A-V block with prolonged P-R interval is seen. Findings at necroscopy showed combined ventricular hypertrophy and dilatation, predominantly of the left ventricle, and apical fibrosis.

The apical electrical forces, usually with an anterior and downward orientation, would be nullified by the fibrosis and would not be opposed to those resulting from the blocked and hypertrophied basal zones with an anterior and upward sense, which would predominate, directing the SÂQRS.

There were no differences between the SÂQRS, SÂT, and terminal 0.04 vectors of 11 analyzed cases of complete left bundle branch block and the commonly found orientation of this type of block occurring in other cardiopathies.

Morphologically, the finding of a Q wave in Leads I, aV_L, and V_5 in cases of complete left bundle branch block was rather frequent (5 instances in 11 cases) (Figs. 4 and 5).

It is necessary to call attention to the fact that these patients were 18, 20, 23, 32, and 37 years old, and that no myocardial infarction or coronary artery lesions except septal and apical fibrosis on microscopic examination were found.

Bilateral "Focal" Block.—In 8 cases the ventricular complexes were predominantly positive in all precordial leads. The ventricular depolarization showed a defect in the conduction of the stimulus (slurred and wide QRS complexes) (Figs. 6 and 7). These morphologic alterations could be interpreted in the right

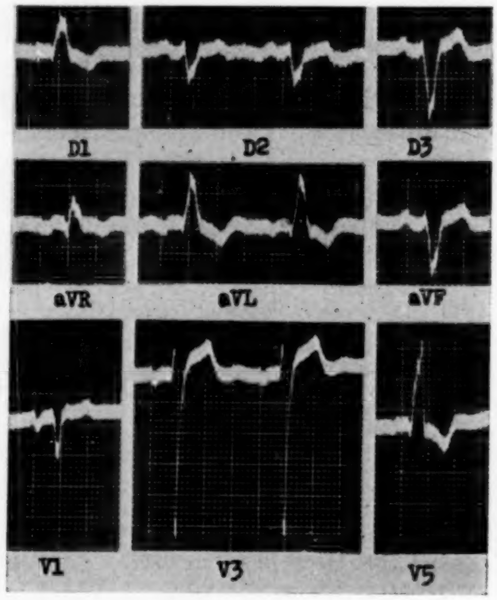

Fig. 4.—Complete left BBB showing Q waves in Leads I, aV_L, and V_5 in a 37-year-old man suffering from Chagas' disease. Autopsy showed septal fibrosis and normal coronary arteries.

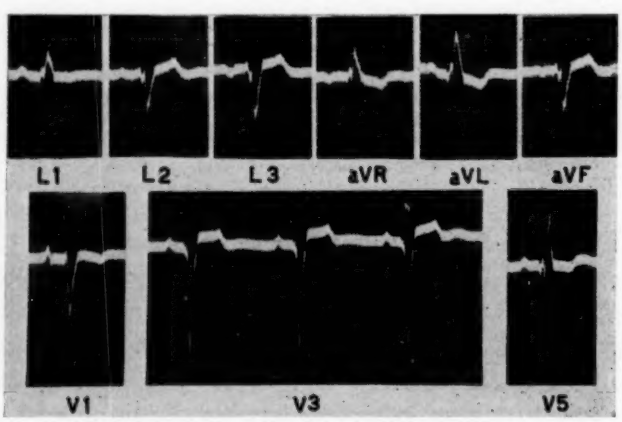

Fig. 5.—Chagas' disease in a 23-year-old man. Electrocardiogram shows a complete left BBB (QRS duration of 0.155 sec. in Lead aV_L) with Q waves in Leads I, aV_L, and V_5, and QS complexes with upward S-T segment deviation in Lead V_3. The pathologic findings revealed extensive apical and septal fibrosis without coronary artery lesions.

precordial leads as right bundle branch block, and in the left precordial leads as left bundle branch block. They were classified by us as bilateral "focal" blocks. Their electrogenesis is of difficult interpretation.[32-34] We could interpret

these morphologic changes as right bundle branch block registered from Lead V_1 to Lead V_6 because of pronounced dilatation of the right ventricle, denying an associated left bundle branch block. We tried to verify at autopsy the existence of a right ventricular dilatation in these cases. In 4 of them the right ven-

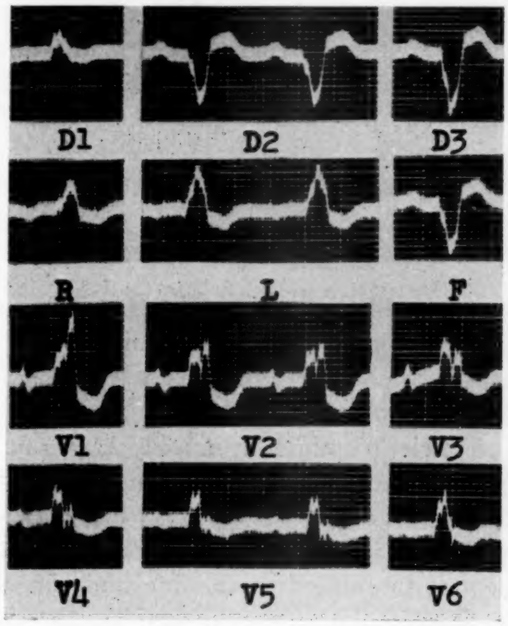

Fig. 6.—Electrocardiogram of a 42-year-old man with chagasic cardiopathy. The QRS complexes are slurred and wide. Leads V_2 and V_3 show two "blocked" regions very clearly. A diagnosis of bilateral "focal" block was made.

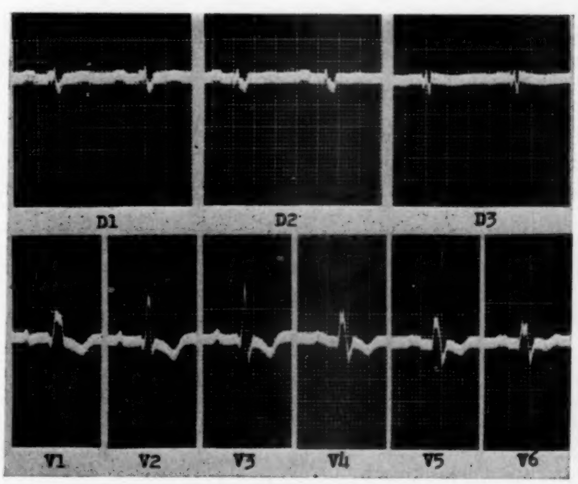

Fig. 7.—Chagas' disease in a 36-year-old man. Electrocardiogram shows signs of A-V block, left auricular hypertrophy, and diffuse disturbance of the intraventricular conduction (bilateral "focal" block ?). At autopsy there was no right auricular dilation nor myocardial infarction that could be related to the presence of the Q waves from Lead V_1 to V_3. Extensive fibrosis was seen microscopically.

tricle was actually markedly dilated, but so was the left; it is doubtful that the right ventricle could displace the left one backwardly and medially. In 3 cases there was a moderate dilatation of both ventricles, and in 1 case a more pronounced dilatation of the left ventricle. It seems to us very unlikely that the abnormal morphology of the QRS complex from Lead V_1 to Lead V_6 could be related to a dilated right ventricle. In some cases it was possible to observe in Leads V_2 and V_3 (Fig. 6) a greater slurring of the middle and terminal portions of the QRS complex. An analysis of these tracings indicates the probable existence of slowings in different portions of the vectorial loop, corresponding to blocked areas in different regions, in one or, more probably, in both ventricles; for this reason we chose the expression "focal" blocks.

SUMMARY

The authors have analyzed the rhythm of 124 electrocardiograms from 103 autopsied patients with chronic chagasic myocarditis.

The most frequent types of arrhythmias were ventricular extrasystoles, atrioventricular block, and bundle branch block.

A higher incidence of right bundle branch block was found, but left bundle branch block was more frequently encountered than usually reported.

Complete right bundle branch block showed a peculiar distribution of ÂQRS between $-60°$ and $-90°$, and terminal QRS vectors between $-100°$ and $-150°$. These orientations seem to be related to the anatomic findings of hypertrophy, dilatation, and apical fibrosis of the ventricles. The presence of right bundle branch block with an upward and left deviation of the ÂQRS, frequently associated with another kind of arrhythmia, is so characteristic in Chagas' disease that if these electrocardiographic signs are found in a young patient with an acquired cardiopathy, they will strongly suggest that we are dealing with chagasic myocarditis, at least in countries where Chagas' disease is endemic.

The vectorial analysis of left bundle branch block was without peculiarities, but Q waves in Leads I, aV_L, and V_5 even in the presence of complete left bundle branch block was frequently found (45.5 per cent).

In 5 of 11 patients showing complete left bundle branch block the ages were 18, 20, 20, 22, and 23 years, respectively.

An electrocardiographic diagnosis of bilateral "focal" block was made in 8 cases showing disturbances of the intraventricular conduction and QRS complexes predominantly positive in all precordial leads.

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A Comprehensive Mapping of Spatial Vectorcardiographic Data

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Vectorcardiography is confronted with two distinct problems: (1) the finding of a proper lead system, and (2) the adequate representation of spatial and temporal events. It is this latter problem which will be treated here. With the aid of a simple instrument and tabulated functions the three scalar components, if recorded simultaneously at a sufficiently high speed, can be utilized to arrive at a comprehensive mapping of the spatial and temporal sequence of cardiac vectors. Such a mapping consists of plane projection loops, as well as spatial magnitude and tilt position curves.

The ordinary electrocardiogram is a two dimensional graph, the horizontal axis representing time, the vertical axis the recorded lead potential. Such traces are referred to as time-based scalar electrocardiograms. The oscilloscopic vector loop is also a two dimensional graph, but here both dimensions are used for the representation of lead potentials, time being abandoned as the horizontal coordinate, the loop being the resultant of a parallelogram of forces of lead potential components. In order to have some indication of time sequence, the loop is interrupted at regular intervals. These plane projection figures, or vector loops, often changing repeatedly in spot velocity and sense of rotation, are far from being quantitively clear. Principally, all defects stem from having sacrificed time as a directional coordinate. Halos and blurring can hardly be avoided if the beam dwells on the same point for a certain length of time. Overlappings of the loop, not only of P and T with QRS, but also of different portions of QRS with each other, are disturbing. Time interruptions suitable for rapidly changing portions will be confluent for slowly changing portions. If two plane projections are recorded simultaneously, which is necessary for a spatial representation, it is difficult and often impossible to identify simultaneous points in the respective planes. In order to overcome these difficulties, the loop has been photographed with a moving film. The resulting figure has temporal and spatial vector components mixed in such a way that a clear insight into the spatial sequence is possible only after a reconstruction by computation. Differential vectorcardiography[1] avoids

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some of the above-stated difficulties by isolating certain portions of the cardiac cycle, but in order to understand the spatial interrelation of P, QRS, and T, it is important to have a full three dimensional information of each complete P-QRS-T cycle. This interrelation can be measured only within one heart beat. Two successive beats are, in the strict sense, not comparable. Abildskov[2,3] recently described a method of obtaining time-based scalar curves containing spatial vectorcardiographic data. He arrives at these curves by means of electronic computers.

The method described in the following finds its justification only in view of the stated demands and difficulties. If plane projection loops displayed on the cathode-ray oscilloscope answered our questions, there would be no need for this method.

METHOD

Recognizing the advantage of the time-based scalar trace for clear visualization of the temporal component, and the advantage of the vector representation for the directional component, we proceed as follows: Three mutually orthogonal bipolar leads, called the horizontal X, vertical Y, and anteroposterior Z axes, are recorded simultaneously on electrocardiographic film* or transparent paper,† as seen in Fig. 1. The lead system employed here is that of Frank modified by Helm.[4] Polarity is such that a positive signal applied to the neck, left side, and back electrodes

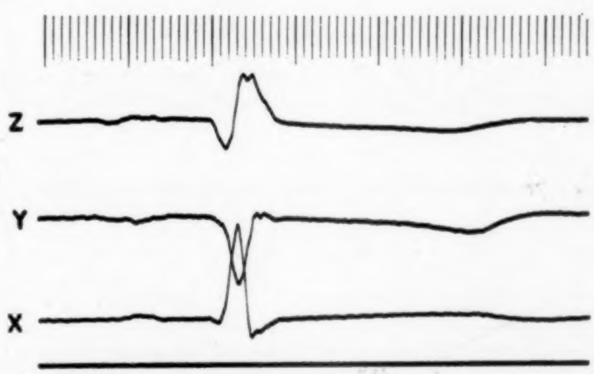

Fig. 1.—Scalar tracing of X, Y, and Z components. Speed, 6 inches per second. Timing lines at 0.01-second intervals.

will result in an upward deflection of the trace on the developed record if it is positioned so that time progresses to the right. In our investigation we use a film speed of 6 inches per second (152 mm. per second) and a deflection of 0.76 cm. per millivolt. The film is projected on a vector drawing instrument designed for this purpose. By an enlargement of 6.55:1 the projected graph is equivalent to 5 cm. per millivolt and 1,000 mm. per second. Standardization and enlargement scales once set are left unchanged. The vector drawing instrument with the projected scalar components X, Y, and Z of Fig. 1 is seen in Figs. 2 and 3. The instrument is mechanically simple. The transparent vertical T square (*A*) with a hairline in the center is brought into parallel alignment with the time lines on the record, which are perpendicular with the static reference trace seen at the bottom of the recorded galvanometer trace. This reference trace will then be parallel to bar *C*. The hairline is moved to the point of earliest onset of QRS, in whichever lead this may

*Eastman Verichrome.
†Du Pont Lino-Writ 4.

be. The movable time marker *B*, a millimeter scale, is brought into a position where the zero point on the scale is in alignment with the indicator of the vertical T square. One millimeter on the scale corresponds to one millisecond on the graph. The time marker *B* is locked, and we proceed to find the successive points of intersection of the hairline with X, Y, and Z. Since the upward or downward displacement of the horizontal lead has to be translated into a right or left

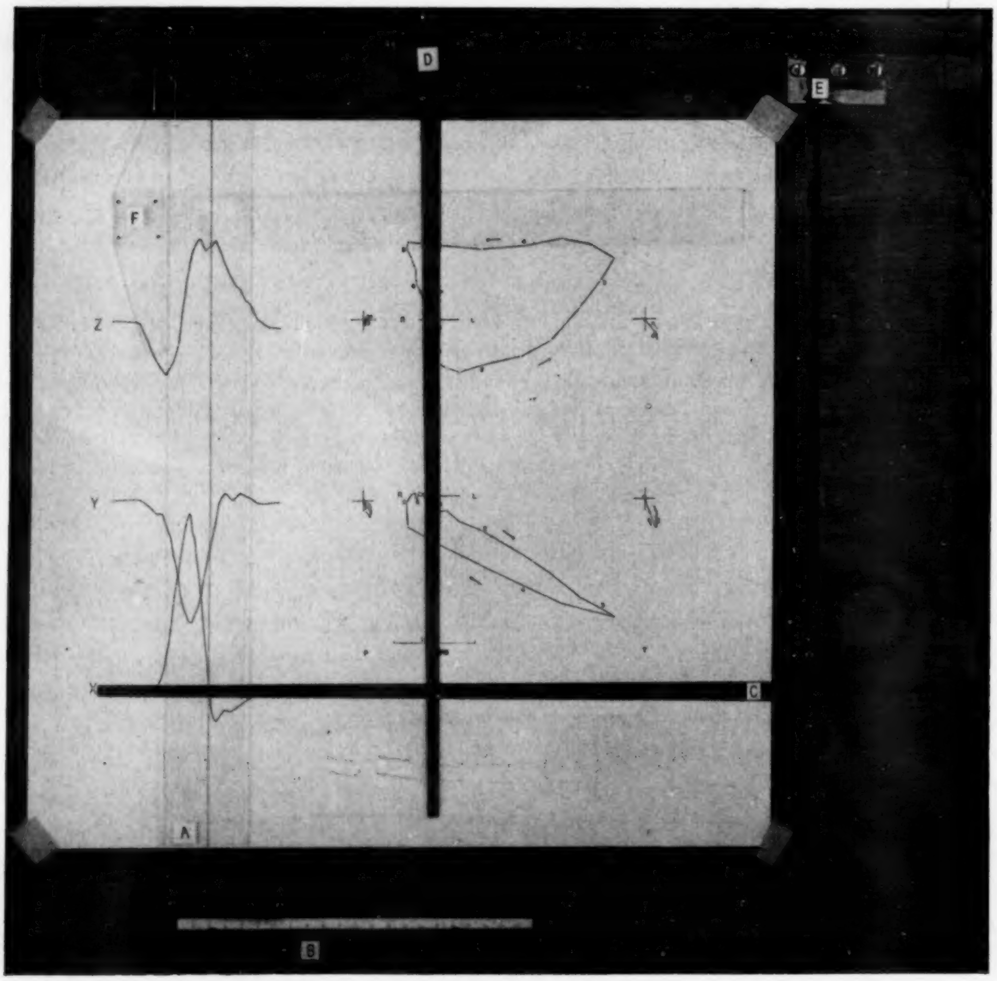

Fig. 2.—Vector drawing instrument. QRS complex of X, Y, and Z of Fig. 1 is projected on the instrument. P, QRS, and T loop plotting has been completed. The instrument is set at 45 msec. of QRS complex. Point of intersection of right edge of *D* and lower edge of *F* gives instantaneous vector-head position of 45 msec. in the horizontal plane. Hairline on *A* is on lower side to avoid parallax.

displacement, a translation device is built into the board, consisting of two perpendicular bars fixed to a set of racks connected by a single gear (*E*). As the horizontal bar *C* is brought to the point of intersection of the hairline and X, bar *D* is automatically carried this distance to the right or left. The point of intersection of the hairline on *A* with Y and Z is carried to the frontal and horizontal plane diagram by the freely movable T square (*F*). The point of intersection of *F* with *D* gives the instantaneous vector-head position for frontal and horizontal planes for the time interval read on the marker *B*. Fig. 2 illustrates the vector plotting of the scalar components of QRS at the time interval of 45 milliseconds (msec.). The plotting can be done at 1.0, 2.5, 5 msec. or at any other desired interval. Irregularities of short duration may be missed in vectordiagrams

spaced at 5 msec. or wider, but the continuous scalar graph is always available for reference, so that any intermediate point at any time interval can easily be determined. QRS duration, ventricular activation time, spatial magnitude curves, instantaneous tilt, or elevation angles can be computed with great accuracy from these graphs. The limitation is given merely by the error factors entering into the lead system. This problem is not discussed here. If the same signal is fed into

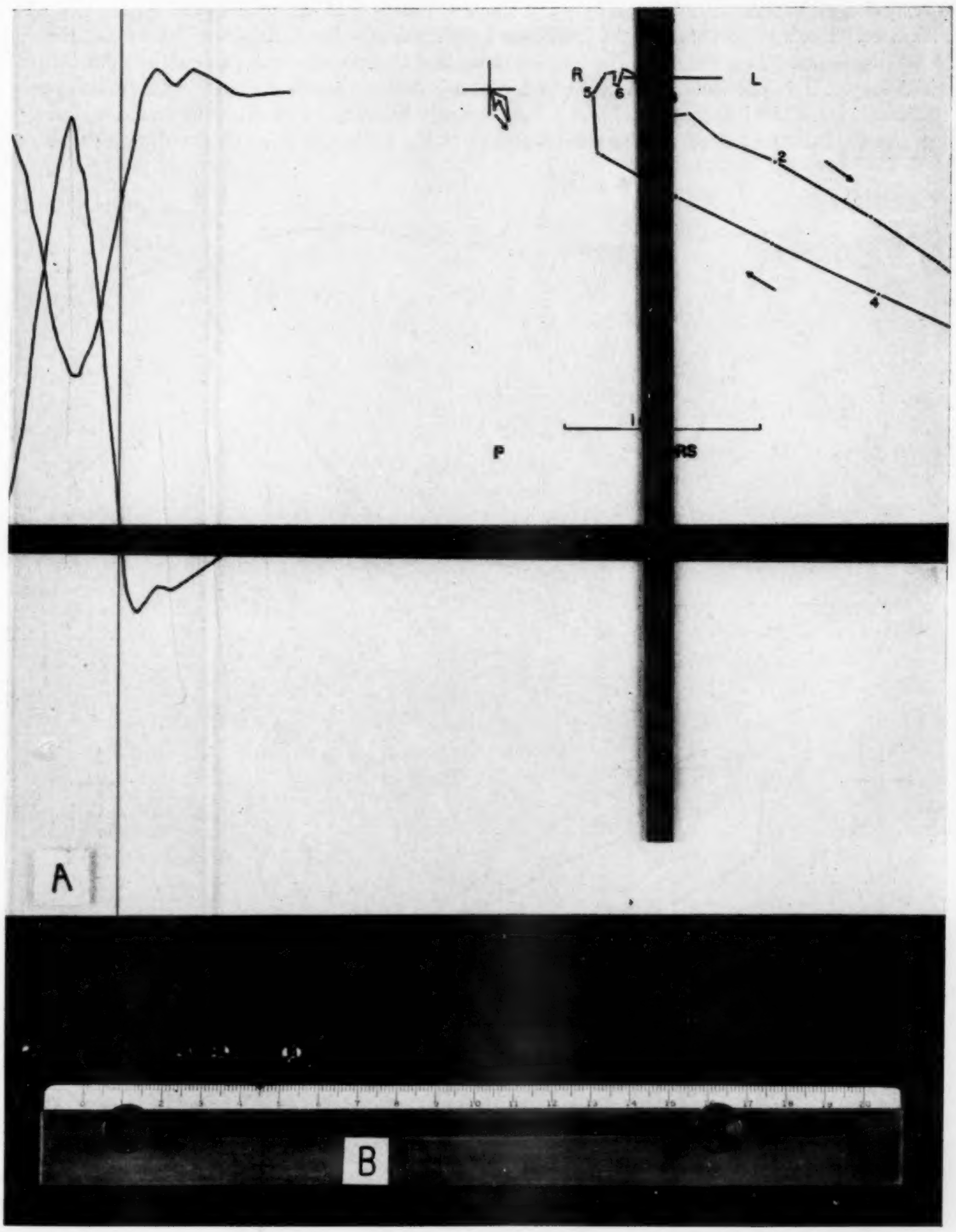

Fig. 3.—Detail showing indicator at 45 msec. on timing scale.

three channels simultaneously, if all three channels are normalized, are free of relative phase distortion, the drawing instrument square and free of parallax, the resultant figure (Lissajous) has to be a straight line with an angle of 45°. This test has always been satisfactory. Fig. 4 shows the frontal and horizontal plane loops of P, QRS, and T as seen in Fig. 2, which is a vector loop of a normal individual. Fig. 5 shows P, QRS, and T loops of a recent inferoposterior myocardial infarction. P, QRS, and T are separated. This is easily done since the racks can be brought into any desired initial position. P is here plotted at intervals of 10 msec., QRS at 2.5 msec., and T at 20 msec. The numbers seen on the QRS loop indicate time value multiples of 10, 1 = 10 msec., 2 = 20 msec., etc. There remains the important task of integrating two plane projections into a spatial loop. It is particularly at this point that we find the method superior to oscilloscopic Lissajous loops. The instantaneous vector is not seen in its spatial magnitude or direction, but in its projection into the frontal and horizontal planes. Only in the exceptional case where a vector is

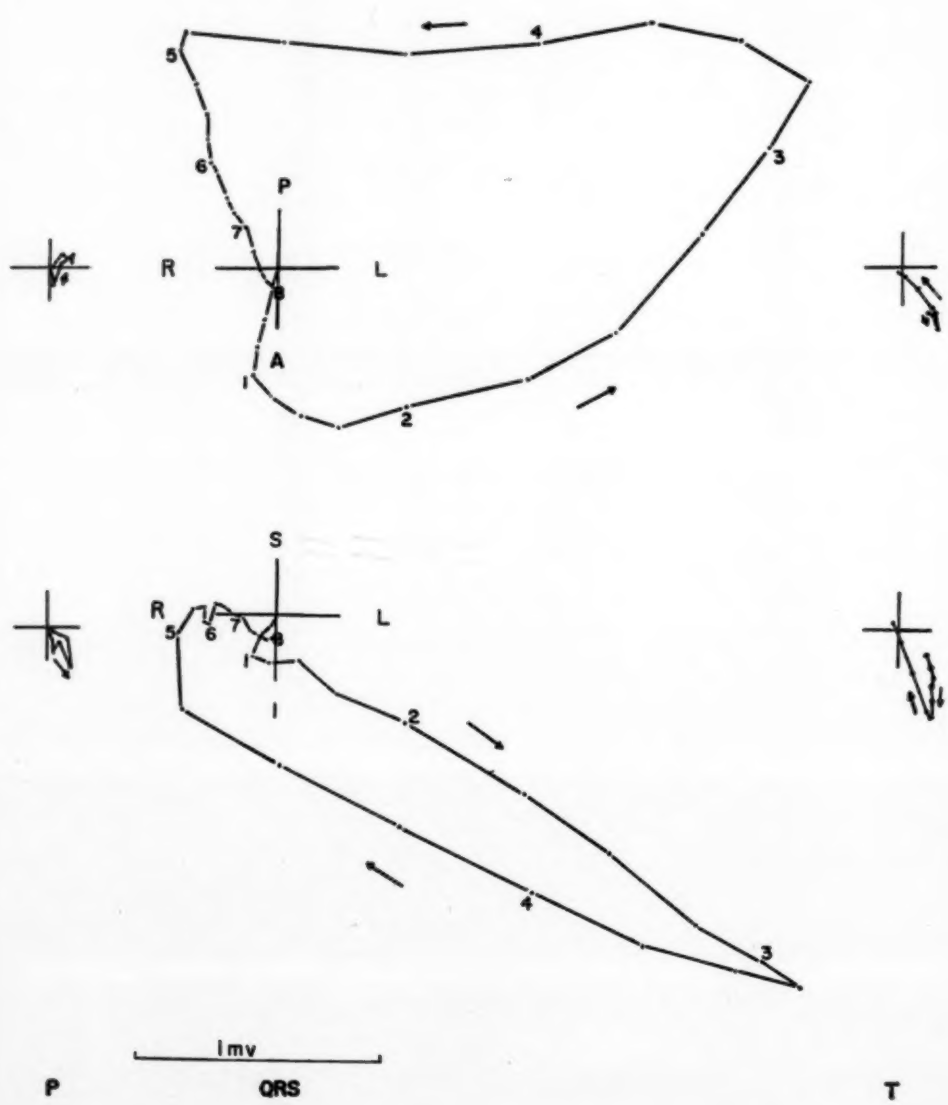

Fig. 4.—Frontal and horizontal plane loops of P, QRS, and T, the same as those seen in Fig. 2.

flush with a plane does such a plane projection give information about spatial magnitude and direction. The direction of the spatial vector is only understood if its two spherical angles, the angle in the frontal plane and the angle of the forward or backward tilt, are known. The frontal plane angle is read directly in the frontal plane projection, but the angle of the tilt is a function of the frontal plane angle and the horizontal plane angle. It cannot be read directly from any plane projection. It can be computed by an equation of transformation which converts Cartesian into spherical coordinates, or it can be read directly from a tabulation[5] of the function cot $T^\circ = \tan \phi^\circ / \cos \alpha^\circ$, where $T^\circ =$ tilt, $\phi^\circ =$ azimuth, and $\alpha^\circ =$ Einthoven's frontal plane angle. Looking at the frontal plane projection of the QRS complex of Fig. 4, we find, for instance, that the vector head at 40 msec. is directed to the left and downward, $\alpha^\circ = +46^\circ$, the simultaneous vector projection in the horizontal plane is pointing to the left and backward, $\phi^\circ = +131^\circ$. Therefore, the resulting spherical angle T° is 31°, which means that at 40 msec. this vector has a frontal angle $\alpha^\circ = +46^\circ$ with

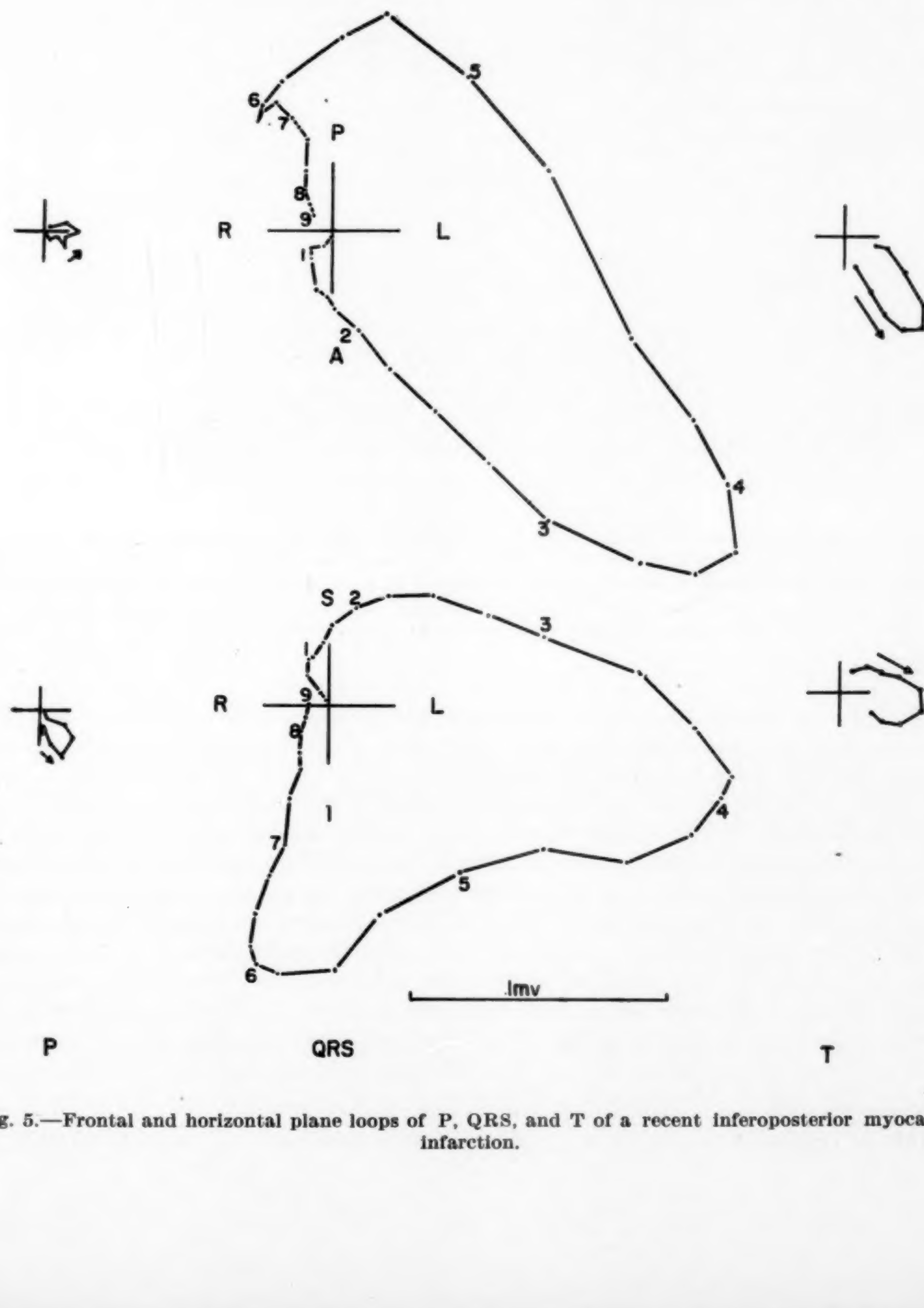

Fig. 5.—Frontal and horizontal plane loops of P, QRS, and T of a recent inferoposterior myocardial infarction.

a backward tilt of 31°.[1] To obtain the spatial magnitude, the frontal plane magnitude is measured and divided by the cosine of the tilt.

Spatial magnitude in millivolts and tilt in degrees, as plotted against time, are seen in Figs. 6 and 7. Neither the spatial magnitude nor the angle tilt are directly visible in multiplane projections, and therefore are an essential supplement to these. The spatial magnitude has, assuming an ideal orthogonal reference frame, the property of being invariant to position. It is the modulus or absolute value of the summation dipole.

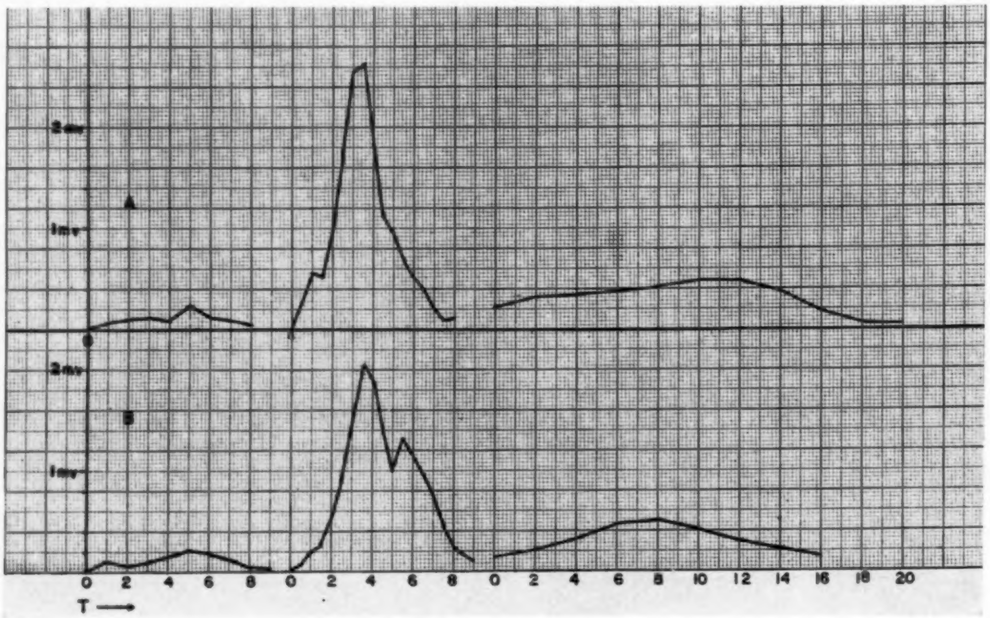

Fig. 6.—Spatial magnitude curves. P plotted at intervals of 10 msec., QRS at 5 msec., and T at 20 msec. *A*, Curve for a normal individual, derived from loops seen in Fig. 4. *B*, Curve for infero-posterior myocardial infarction, derived from loops seen in Fig. 5. P-R and S-T intervals are not plotted.

INSTRUMENTATION

The scalar tracings, as seen in Fig. 1, are recorded with a multichannel recording oscillograph,* using d'Arsonval type mirror galvanometers (Type 7-362). The galvanometers are fluid damped with a natural undamped frequency of 4,150 cycles per second (c./s.) and a linear response of 0 to 2,500 c./s. The amplification system consists of a DC electronic inverter type amplifier† and a matching AC preamplifier filter network between the patient and the input of the inverter amplifier. The filter network contains selective high and low cutoffs. At maximum band-width setting the whole system, including amplification and galvanometers, has a linear frequency response from 0.1 to 2,500 c./s. Time constant is 8 seconds. Input is differentially balanced with an impedance of 20 megohms. Gain can be adjusted from 0 to 10 inches per millivolt if AC-DC coupled, or from 0 to 3 inches per millivolt if DC amplification only is desired. The recording camera of the galvanometer oscillograph has a speed range from ¾ in./sec. to 24 in./sec. in six steps. A DuMont cathode-ray oscilloscope (Type 401) is used for monitoring either scalar tracings or

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***Consolidated Electrodynamics Corporation, Type 5-117.**

†Alinco, Type 307-A.

vector loops. The tracing seen in Fig. 1 is recorded at maximum band-width setting. Except for cases of extreme tremor, we find no need for cutoff filters in vectorcardiographic work. The initial portion of QRS can always be seen clearly in this method, because there is no overriding and halo problem.

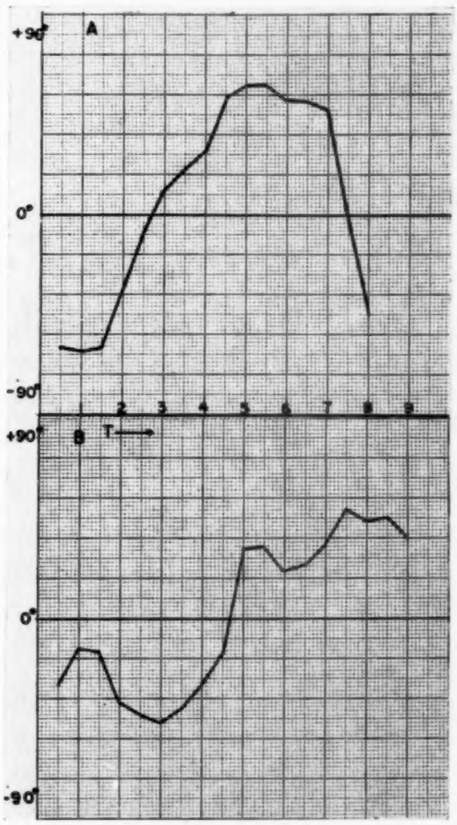

Fig. 7.—Tilt (cot T° = tan ø°/cos α°) of QRS complex plotted against time at 5-msec. intervals (− indicates forward tilt and + indicates backward tilt). *A*, Normal curve derived from loops seen in Fig. 4. *B*, Curve for inferoposterior myocardial infarction derived from loops in Fig. 5.

SUMMARY

High-speed, simultaneous film recording of the scalar components X, Y, and Z is used for plotting vector loops with accurate spatial and temporal representation. Such loops are used for computing spatial magnitude and tilt position curves which are an essential supplement to plane projection loops. A brief description is given of the recording instrument which has a wide frequency and speed range.

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TsÊ Loop in Left Ventricular Hypertrophy

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The hypertrophy of the left ventricular wall without having caused any determinable dilatation of the heart's silhouette in the x-ray picture intra vitam is a familiar feature to the pathologist. Clinical manifestations of initial left ventricular hypertrophy are, however, not easily listed. There are sometimes a multitude of symptoms, whereas the condition has occasionally been found to exist not only symptomless but also in combination with an excellent heart function, as for instance in athletes. It is highly probable that left ventricular hypertrophy is much more common than has been suggested hitherto by the clinicians. Its diagnosis gains still more in importance since the prognosis of the actual condition is very much dependent upon whether left ventricular hypertrophy is present or not.

The increase of the roentgenologic heart volume, including also the dilatation of the cavities, does not reveal, even approximately, the thickness of the muscular layer of the left ventricle. However, hypertrophy of the muscular wall is the initial factor in the process, precursor to the manifest increase in the volume. It coincides frequently with arterial hypertension, but very irregularly, and this circumstance does not yield any acceptable ground for its diagnosis.

The diagnosis of myocardial hypertrophy has been one of the most central subjects in the vectorcardiographic literature of the past decade. Vectorcardiographic diagnosis of hypertrophy of the left ventricle, as opposed to that of the right, is very complicated.

In their comparative electro- and vectorcardiographic study, Braunwald and co-workers[4] found that the electrocardiographic criteria for the diagnosis of left ventricular hypertrophy given by Sokolow and Lyon,[16] which include all known electrocardiographic patterns encountered in the preponderance of the left ventricle, were unsatisfactory. In their series of left ventricular hypertrophies due to congenital heart disease these criteria were applicable in 32 per cent only. These authors state that there is apparently a great number of patients who have left ventricular hypertrophy due to congenital heart disease, but who present normal electrocardiograms. They also conclude that the de-

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termination of the electrical axis was of little value in the diagnosis of ventricular hypertrophy, and consider that abnormal voltages and ventricular activation times are more reliable as diagnostic criteria.

The merits of vectorcardiography for the detection of left ventricular hypertrophy are markedly better, although it failed in 12 out of 28 cases. The entire material comprised 135 patients with congenital heart lesions. In the interpretation of the vectorcardiograms the above authors paid attention mainly to the spatial localization of the QRSsÊ and TsÊ loops. The shape of the first-mentioned loop was considered particularly with special reference to the mutual relations of its different parts, as well as to the direction of the rotation of the QRS vector head. A circumstance noted from the TsÊ loop was the spatial relation of its axis to that of the QRSsÊ loop.

According to Grishman and Scherlis,[7] vectorcardiographic recording affords an aid in differentiating LBBB from left ventricular hypertrophy. In 20 persons with left ventricular hypertrophy no delay in activation time could be established from the QRSsÊ loop. However, in 10 of these persons, the authors were able to record an activation retardation in esophageal leads, corresponding to the posterobasal surface of the left ventricle as compared with the anterolateral aspect. No particular attention was paid to the appearance of the TsÊ loop.

However, our increasing understanding of the nature of repolarization makes it justifiable to apply quite new aspects to the TsÊ loop. These are the mutual time relations of the repolarization potentials of different lead axes, which are manifestly yielded by the TsÊ loop. It has been maintained previously that localized myocardial lesions and myocardial damage due to hypercholesterolemia may be clearly disclosed from the imbalance of the repolarization potentials of the TsÊ loop, even when the electrocardiograms are uninformative.[8,9]

Since the multidirectional repolarization waves show mutual time differences, and recent investigations have estimated the elapsed time for normal repolarization between endo- and epicardial surfaces of the left ventricle, these facts have been taken into account in the present study for the judgment of left ventricular hypertrophy.

INTRODUCTION

It has long been clear that there is an intimate relationship between the depolarization (QRS) and repolarization (T) of the myocardium. However, the problem of repolarization in its entirety has been very hard to approach electrocardiographically. The difficulty of determining with precision the limits and summit of the T wave has greatly complicated this investigative task. Similarly, the distinct estimation of the Q-T time, which has recently regained in interest, is attended by great difficulty, even with the different devices and equations that have been recommended. Yet, despite the intricate nature of the problem, basic knowledge had been acquired already in the early twenties as to the inhomogeneity of the repolarization process, or recovery process, as it is also called. It was realized that the duration of the excitation in the left ventricular wall exceeded that in the right. Futhermore, it was found that the

repolarization potential can be influenced by local physical agents, such as temperature changes, or by the activation process. The former lead to primary, the latter to secondary, T-wave changes.

The prevailing opinions on the repolarization process eventually led to the vector conception. It was introduced by Wilson and co-workers[17] and by Ashman,[1] and was called "ventricular gradient." In terms of voltage and time it is considered to express the order of recovery in the myocardium. Consisting of the areal summation of voltage and time of de- and repolarization from two extremity leads, the ventricular gradient is influenced by the difference of the respective waves.

Since it is difficult to state exactly the Q-T intervals of the leads in question, their mutual correlation is not sufficiently efficient and excludes the phase shift effect from the ventricular gradient. Nor are the S-T displacements reflected adequately from the ventricular gradient vector. Undoubtedly, they influence the subsquent T wave, the areal change of which will be hard to plot precisely. Therefore, in hypoxemia and exercise tests, even significant changes in the S-T interval and T wave may fail to alter the frontal plane ventricular gradient. In his series of 15 patients, Biörck[2] reported 2 cases without any change in the ventricular gradient after an hypoxemia test, in spite of a marked electrocardiographic reaction with depression of the S-T interval. A third patient showed a paradoxical reaction, the ventricular gradient suggesting that there was an improvement in the ischemic state, although the electrocardiogram pointed to increased hypoxemia with S-T depression. Although the ventricular gradient reflects changes in the S-T interval indirectly through the transfiguration of the subsequent T wave and altered Q-T time, it is questionable whether the ventricular gradient is adequate for interpretation of ST-T changes of the character mentioned. The ventricular gradient undoubtedly gives valuable information as to the direction of the recovery process in the myocardium. It is debatable, however, whether the apparently minute transfigurations of the respective QRS complexes and T waves, and their changed mutual time differences in the ECG leads in question, can be characterized with sufficient exactness by the ventricular gradient vector. Furthermore, the interpretation is complicated through its unlimited possibilities in size, direction, and spatial relationship to the QRS and T vectors. As distinguished from the spatial Ts$\hat{E}$ loop the ventricular gradient, being a single vector, announces the direction of the recovery process, whereas the former is the product of potential variations as time function during the recovery process. In addition, it may be mentioned that similar changes in the ventricular gradient vector may be produced by left ventricular hypertrophy, anoxemia, and myocardial infarction. The lack of satisfactory preciseness and the time-consuming measurements necessary for its estimation have limited its practical use.

In recent times, experiments carried out by Prinzmetal and co-workers[13,14] proved the existence of time difference of repolarization potentials. Contrary to the previous opinion that the direction of repolarization is the reverse of that of depolarization, i.e., from epicardium to endocardium, these authors were the first to demonstrate that its time course, in 59 out of 69 experiments, was from

subendocardium to epicardium. This time delay occurred independently of the polarity of the T wave. Time difference could be observed also between the repolarization potentials from the apex and base of each ventricle. In the left ventricle the apical T wave preceded that from the base by 0.003 second, the relation being reversed in the right ventricle. The mean time difference in the left ventricle alone was 0.007 second, the subendocardial layer preceding the epicardium. Furthermore, the repolarization recorded from the surface of the right ventricle preceded that from the surface of the left ventricle. In each instance time measurements in these experiments were related to the apices of the T waves.

The direct recording from different points of the surface of the heart produces a multitude of T-wave types. The large scatter in repolarization potentials from adjacent areas occurs seemingly without rules, and therefore causes confusion when the appearance of semidirect records are judged. Probably, adjacent fibers display different curves. Anyhow, the laws governing the near-field effect are still unknown. This problem is intimately connected with the question of whether a single unipolar potential is to be considered solely as an intrinsic deflection, or whether it also includes extrinsic components. Without any great risk of error it may be concluded that the remote electrode records a complexity of repolarization potentials. The manifest T wave may be considered as integration of potentials with different time course. However, the mutual influence of near-field effect and remote potentials takes place under unknown conditions. An additional complicating factor is the difference in shape of the monophasic action potentials of different fibers. The difference concerns speed and form of the repolarization potential. According to Hecht, there are at least three types of repolarization velocity amongst the fibers. It is to be observed that the repolarization of the membrane displayed by the monophasic action curve represents a part of the fiber function. The repolarization must be adapted harmoniously to the systolic and diastolic action of the fiber provided by the undisturbed work of the heart muscle, in harmony with correct time relation with other fibers. This work is greatly influenced by physical factors. As shown by Lepeschkin,[11] the temperature of the blood inside the ventricular cavities is 1 to 2° F. cooler than intramurally. This is supposed to be responsible for the longer duration of action in the subendocardial layer, i.e., for later repolarization. Consequently, the ventricular gradient in such case points from the cavity to the surface. However, the aforementioned experiments of Prinzmetal and co-workers support the view that the time course of repolarization is the reverse in most instances.

Further advance in the knowledge of repolarization entails the determination of relative quantities of electrical energy generated during de- and repolarization. According to Kossmann and co-workers,[10] an opinion of this may be gained by dividing the electrical energy expended during depolarization with that of repolarization. The work done during each phase can be calculated from the QRSsÊ and TsÊ loops, and is given in terms of microvoltseconds. By taking notice of the area of the TsÊ loop in the calculation, the effect of phase shift of the repolarization potentials from different myocardial parts will be incorporated. Naturally, this is possible only when the loops are obtained from the cathode-ray

screen. In graphically synthetized vector loops, minute time shifts will not be efficient. Since it has become manifest that repolarization occurs asynchronously, there has not been any more adequate means of approaching this phenomenon than the spatial TsÊ loop. It has been shown by many authors that this loop is normally narrow. Generally, its efferent limb cannot be distinguished from the afferent one. The maximal vector or long axis determines the shape of the loop.

Kossmann and associates state that the electrical energy expended during depolarization is equal to that used by repolarization. This means that the areas of de- and repolarization multiplied by the respective times are equal. It is quite easy to estimate both these areas, and, as concerns repolarization, the vectorcardiographic method offers the only possible means of estimating exactly its duration as well as its voltage at each instant. This is due to the easily determinable origin and termination of the TsÊ loop. Normally, these points join together. When there is a residual potential after the completed depolarization, the TsÊ loop is unclosed. In both cases the differentiation of the TsÊ loop can be made distinctly.

When there is a retardation of repolarization potentials from certain parts of the myocardium, a phase difference will occur, causing a corresponding increase in the breadth of the TsÊ loop. Simultaneously, its long axis decreases. If the TsÊ loop is now compared with an ellipsoid figure, the newly formed maximal breadth of this figure represents its short axis. This may be given in percentage of the long axis. In this way the degree of the relative retardation can be determined approximately. Normally, the phase difference during the repolarization process is inconsiderable or practically absent, i.e., homonymous points will be recorded by the perpendicular leads almost simultaneously. When the retardation is present, it is possible to determine the localization of the decreased conductivity from the direction of inscription of the TsÊ loop. The fact that there is a lack of phase difference in the TsÊ loop of any vectorcardiographic lead combinations in normal cases seems to afford the advantage that the electrocardiographic lead components may be chosen quite arbitrarily. The author of the present paper has gained the impression that, normally, no phase difference exists independently of the two leads employed, and recent investigations confirm this. This makes it possible to search for two electrocardiogram components which produce maximal phase shift. In the future, this could possibly liberate vectorcardiography from the necessity of employing fixed lead systems. Anyhow, at present the determination of phase shift recognizable from the TsÊ loop of frontal, sagittal, and horizontal plane projections obtained by Goldberger's lead system, or from the TsÊ loop of the vectorcardiographically combined precordial leads, accurately reveals delayed or ceased conductivity of the myocardium.

It may be stated conclusively that, despite difficulties of detailed approach to the problem, it seems to be proved that the time differences occur in the repolarization potentials from different parts of the myocardium. The phase shift in the TsÊ loop is the vectorcardiographic evidence of the existing mutual time dif-

ferences. Although experimental proof exists which points to the propagation of the recovery process from the subendocardial toward the subepicardial layer and from the apex to the base of the left ventricle, this subject is still a debated one.

Nevertheless, the repolarization time course is of minor importance for the diagnosis of unilateral left ventricular hypertrophy; in this condition it is of importance to indicate the existing time delay of the repolarization through the hypertrophied muscular layer, independent of its course. Since there is proof of the applicability of the vectorcardiographic recording in the diagnosis of local impairment of the myocardial conduction, and since it is highly probable that the time difference of the repolarization potentials in subendocardial and epicardial layers is much more marked in left ventricular hypertrophy than in normal cases, the phase difference in the TsÊ loop has been employed in the present study. Results have been compared with electrocardiograms and clinical findings.

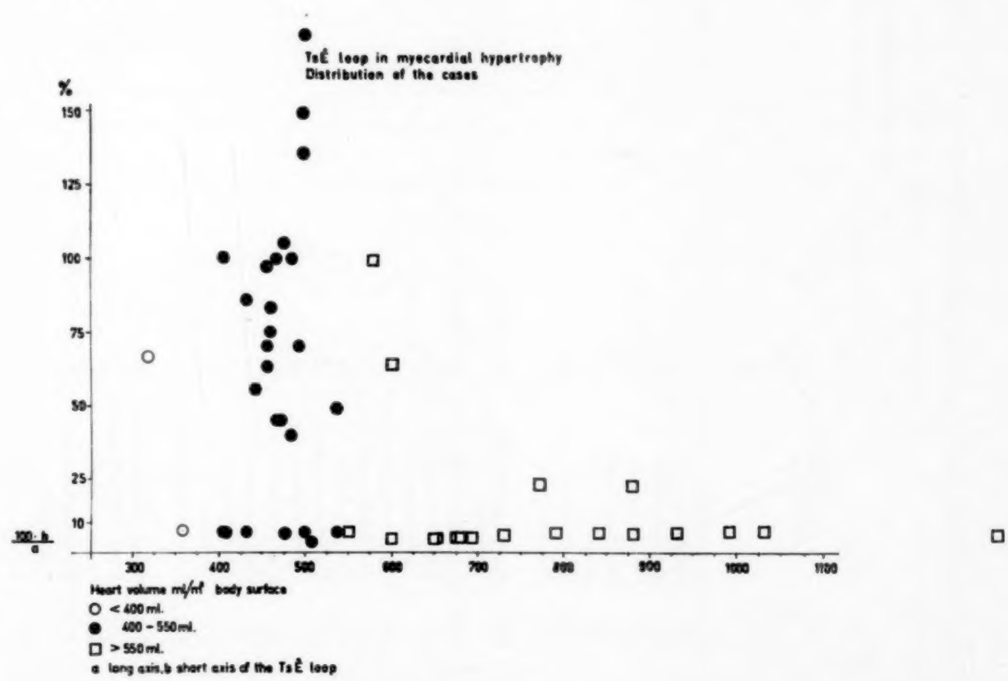

Fig. 1.—The distribution of cases according to roentgenologic heart volume (X axis) and to phase difference recognizable from the TsÊ loop (Y axis).

MATERIAL AND METHODS

The total material consisted of 47 cases of assumed left ventricular hypertrophy, 31 males and 16 females; the average age of the entire series was 61.6 years. Nine instances were within normal limits of the roentgenologic heart volume. In 12 cases the diagnosis was made vectorcardiographically from the appearance of the TsÊ loop, before any evidence of roentgenologic enlargement of the heart occurred. In 11 of these 12 cases the increase in the heart volume was subsequently proved roentgenologically. Heart volume was estimated according to the method introduced by Lysholm.[12] It was calculated as related to the body surface and is given in milliliters per square meter of body surface. The normal upper limit was considered to lie at 450

TABLE I. THE MOST RELEVANT CLINICAL, ROENTGENOLOGIC, ELECTROCARDIOGRAPHIC, AND VECTORCARDIOGRAPHIC DATA OF THE MATERIAL

CASE	SEX	AGE (YR.)	SUBJECTIVE SYMPTOMS	BLOOD PRESSURE (MM. Hg)	HEART VOLUME (ML./M.^{2} BODY SURFACE)	CLINICAL DIAGNOSIS	ELECTROCARDIOGRAM						VECTORCARDIOGRAM					
							RHYTHM	QRS	LEFT AXIS DEVIATION	SPLITS	S-T	T	LEFT AXIS DEVIATION	HF	dA QRS-T	PHASE SHIFT IN TSÊ LOOP $\left(\frac{100 \cdot b}{a}\%\right)$	PLANE OF MAXIMUM PHASE SHIFT	POTENTIAL OF INJURY
1.	M	57	Orthopnea	130/80	460	Cardiosclerosis	SR									70	S	
2.	M	69	None	125/65	460	Duodenal ulcer	SR						+	+		65	F	
3.	F	81	Fatigue	115/65	480	Cardiosclerosis	AF	LBBB	+	+		I, II, V_{5-7} neg.	+	+	disc.	100	F	+
4.	M	78	None	200/110	430	Duodenal ulcer	SR						+		disc.	85	S	+
5.	F	63	Dyspnea	130/90	470	Aortic stenosis	SR		+		↓ I, II, V_{5-7}	I, II, V_{5-7} neg.	+		disc.	45	S	+
6.	M	70	None	125/70	470	Cholelithiasis	AF		+				+	+		100	F	
7.	M	72	Claudicatio intermittens	130/80	490	Arteriosclerosis	SR						+	+		70	F	
8.	M	64	Angina pectoris	165/115	580	Healed myocardial infarction	SR	Q_{II-III}				I, V_{4-7} neg.	+		disc.	100	F	+
9.	M	49	Dyspnea	130/80	410	Neurosis cordis	SR	High voltage V_{5-6}								100	S, H	
10.	M	70	Angina pectoris	210/120	470	Healed myocardial infarction	SR					V_1 diphasic, I, V_{2-7} neg.	+			45	S, H	
11.	M	57	Gastric discomfort	180/85	550	Cardiosclerosis	SR					I, III, V_{2-7} neg.			disc.	0		
12.	M	56	Anginal pain	125/65	410	Cardiosclerosis	SR						+			0		
13.	M	39	Anginal pain	140/90	410	Neurosis cordis	SR						+			0		
14.	M	56	Dyspnea	120/80	430	Asthma bronchiale	SR									0		
15.	F	51	Epigastric pain	170/100	500	Cushing syndrome	SR		+	+	↓ I, V_{1-5}	I, III, V_{5-7} neg.	+	+	disc.	0		
16.	F	67	None	200/80	540	Diabetes mellitus	SR		+	+	↓ I, II, V_{4-7}	I, II, V_{5-7} neg.	+		disc.	0		
17.	M	69	Dyspnea	130/80	480	Healed myocardial infarction	SR	Q_{II-III}	+	+	↑ V_7	II-III neg., V_5 diphasic, V_7 neg.		+	disc.	0		
18.	M	52	Epigastric discomfort	180/100	500	Cirrhosis hepatis	SR		+		↓ I, III, V_{2-7}				disc.	0		
19.	F	75	Dizziness	180/100	460	Arterial hypertension	SR		+			V_{2-3} isoelectric, V_{4-7} diphasic	+		disc.	75	F, H	+
20.	F	66	Angina pectoris	240/105	790	Arterial hypertension	SR		+		↓ I, II, V_4	I, II, V_4 neg.	+		disc.	0		+
21.	F	60	Dyspnea	255/150	1,030	Arterial hypertension	SR		+		↓ I, III, V_{4-7}				disc.	0		+
22.	M	66	Dyspnea	205/110	540	Cardiosclerosis	SR	>0.10 sec.			↓ V_{4-7}					50	F, S	
23.	M	49	Precordial pain	120/80	360	Healed myocardial infarction	SR	Low voltage I-II					+			0		

24.	M	48	Fatigue	140/100	440	Arterial hypertension	SR									60	S	
25.	M	64		200/100	480	Cerebral accident	SR				↓ I, II, V_{4-7}					35	S	
26.	F	59	Angina pectoris	170/110	990	Acromegalia	AF		+		↓ V_{4-7}		+		disc.	0		
27.	M	60	Precordial pain	180/105	680	Healed myocardial infarction	SR	Q_{II-III}	+			I, II, V_4 neg.	+		disc.	0		
28.	M	70	Precordial pain	140/75	840	Cardiosclerosis	SR	Q_{AVF}	+			II, aV_F neg.	+		disc.	0		
29.	M	72	Dyspnea, edema	185/90	880	Cardiosclerosis	AF	>0.10 sec.			↓ I, II, V_{5-7}		+	+	disc.	0-100	F	
30.	M	69	Angina pectoris	160/80	770	Cardiosclerosis	SR	>0.10 sec.			↓ V_{5-7}		+	+	disc.	20-30	S, F	+
31.	M	54	Dyspnea	200/105	880	Cardiosclerosis	SR	LBBB							disc.	20-30	F	
32.	F	70	None	160/100	600	Cardiosclerosis	SR								disc.	0	(small TsÊ loop)	
33.	F	45	None	165/100	650	Cardiosclerosis	AF				↓ I, II				disc.	0	(small TsÊ loop)	
34.	F	68	Tachycardia	130/80	680	WPW syndrome	SR		+		Pre-excitation		+		disc.	0		
35.	M	37	Headache	130/80	330	Cephalalgia	SR									70	S, H	
36.	M	64	Dyspnea	270/105	660	Arterial hypertension	SR		+			I, II, V_{1-7} neg.	+		disc.	0		
37.	M	60	Dyspnea, edema	205/130-115	690	Arterial hypertension	AF				↓ I, III, V_{4-7}		+	+	disc.	0		+
38.	M	55	Dyspnea, precordial pain	130/80	600	Healed myocardial infarction	SR	QS_{V1-4}	+		↓ V_7	I, V_7 low			disc. ±	60	S	
39.	M	65	Dyspnea	240/120	730	Arterial hypertension	AF				Total A-V block				disc.	0		+
40.	M	49	Tachycardia attacks	115/80	450	WPW syndrome					Pre-excitation			+		80	F	+
41.	F	64	Dyspnea, edema	170/80	1,320	Nephropathia	AF				↓ I, II, V_{4-7}		+		disc.	0		+
42.	M	69	Anginal pain	220/100	440	Hypercholesterolemia	SR		+						disc.	80	S, H	+
43.	F	66	Dyspnea	210/100	930	Diabetes mellitus Arterial hypertension	SR		+		↓ I, II, V_{5-7}	V_{5-7} neg.	+		disc.	0		+
44.	F	73	Tachycardia, dyspnea	220/100	500	Aortic stenosis	SR		+		↓ I, II, V_{4-7}	I, II, V_{4-7} neg.			disc.	200	H	+
45.	F	45	Anginal pain	130/70	500	Cardiosclerosis	SR			+	↓ V_7	V_7 diphasic			disc. ±	140	H	+
46.	M	63	Anginal pain	160/95	500	Hypercholesterolemia	SR								disc. ±	130	S, H	+
47.	F	74	Anginal pain	210/110	480	Arterial hypertension	SR		+		↓ I, II, V_{5-7}	I, II, V_{4-7} neg.	+		disc. ±	110	F	+

HF = high frequency.
a = short axis, b = long axis of the TsÊ loop.
F = frontal, S = sagittal, and H = horizontal plane projection of the vectorcardiogram.
AF = auricular fibrillation.
SR = sinus rhythm.
disc. = discordant.

ml./M.² of body surface. In the present study, in which special attention was paid to the diagnosis of the initial hypertrophy of the left ventricular wall, the material was divided into three different groups. Cases of roentgenologic heart volume of less than 400 ml./M.² of body surface formed a group in which the hypertrophy of the myocardial wall was probably absent. The second group represented cases from near the normal upper limit and up to the moderate increase of the roentgenologic heart volume (400 to 500 ml./M.² of body surface). Finally, there was a third category composed of cases with roentgenologic heart volumes above 550 ml./M.² of body surface. Vectorcardiograms obtained from 54 healthy individuals, 25 males and 29 females, ranging in age from 18 to 69 years, were used as a control group.

The apparatus as well as the method for obtaining the vectorcardiographic curves were described earlier.[8] In the analysis of the vectorcardiogram special attention was paid to the following details: (1) *Left axis deviation*. This was estimated from the frontal plane projection only. Left axis deviation was considered to be present when the maximal vector of the QRSsÊ loop made an angle of less than 30° with the horizontal plane. (2) *High-frequency details*. These are rapid oscillations of undulatory or bending character in the course of the QRSsÊ loop. Cases showing high-frequency details have been reported separately. (3) *The deviation angle between the maximal vectors of the QRSsÊ and TsÊ loops.* Annotations were made of the existing concordance or discordance between these vectors. Values above 60° of the spatial angle (T-QRS) were considered as discordant. In cases where the TsÊ loop was nearly circular on account of phase shift, its maximal vector was hard to plot. These cases are designated *disc.*± in Table I. (4) *The phase shift of the repolarization potential.* This was determined from the TsÊ loop by estimating the maximal length (a) and short axis (b) of the loop in question. The degree of the phase shift was calculated by estimating the percentage of the short axis from the length axis. (5) *Plane or planes of maximal phase shift.* These were observed. (6) *Residual potential after completion of depolarization.* Notice was taken as to whether or not such a residual potential existed.

Vectorcardiographic records were compared with electrocardiographic and clinical findings. Table I gives all data of interest in the present study. Fig. 1 shows the distribution of the cases according to the roentgenologic heart volume and degree of phase difference observable from the TsÊ loop.

The results are presented as four diagnostic groups: (A) Hypertensive Disease. (B) Aortic Valvular Disease. (C) Cardiosclerosis. (D) Various Conditions. In all these groups there was a considerable left ventricular stress. The fourth group was made up of various clinical conditions with clinical, electrocardiographic, and/or vectorcardiographic signs of left ventricular hypertrophy. In each group the material was divided into three categories according to the roentgenologic heart volume. All cases with a diastolic blood pressure ≧ 100 mm. Hg were classified as Group A.

RESULTS

A. *Hypertensive Disease.*—Arterial hypertension was established in 23 instances, with the mean roentgenologic heart volume of 600 ml./M.² of body surface. The corresponding figure for the entire series was the same.

Electrocardiogram: Twelve of these 23 patients presented left axis deviation in the electrocardiogram. In 5 cases there were changes in T waves as an isolated phenomenon. S-T depression was present in 7 cases, and in 5 there were both S-T depression and inverted T waves in the leads over the left ventricle. Consequently, there were changes in the entire S-T-T segment in 17 instances. In one case, there was atrioventricular dissociation, in another left bundle branch block, and in a third left axis deviation as an isolated phenomenon. In 3 cases the electrocardiogram was normal.

Vectorcardiogram: The maximal vector of the QRSsÊ loop of the frontal

plane projection showed left axis deviation in 12 cases. Discordance between the maximal vectors of the QRSsÊ and TsÊ loops was present in 19 of 23 patients.

The phase difference of repolarization potentials was present in 11 cases, with the mean value of 80 per cent when the increased length of the short axis of the TsÊ loop was compared with its long axis. The mean roentgenologic heart volume in the group with phase shift in the TsÊ loop was 520 ml./M.² of body surface. The corresponding figure for the 12 remaining cases without any phase shift was 730 ml./M.² of body surface.

The residual potential difference, or potential of injury, was present in 11 cases, representing a mean value of the roentgenologic heart volume of 640 ml./M.² of body surface, and a mean phase difference in the TsÊ loop of 60 per cent.

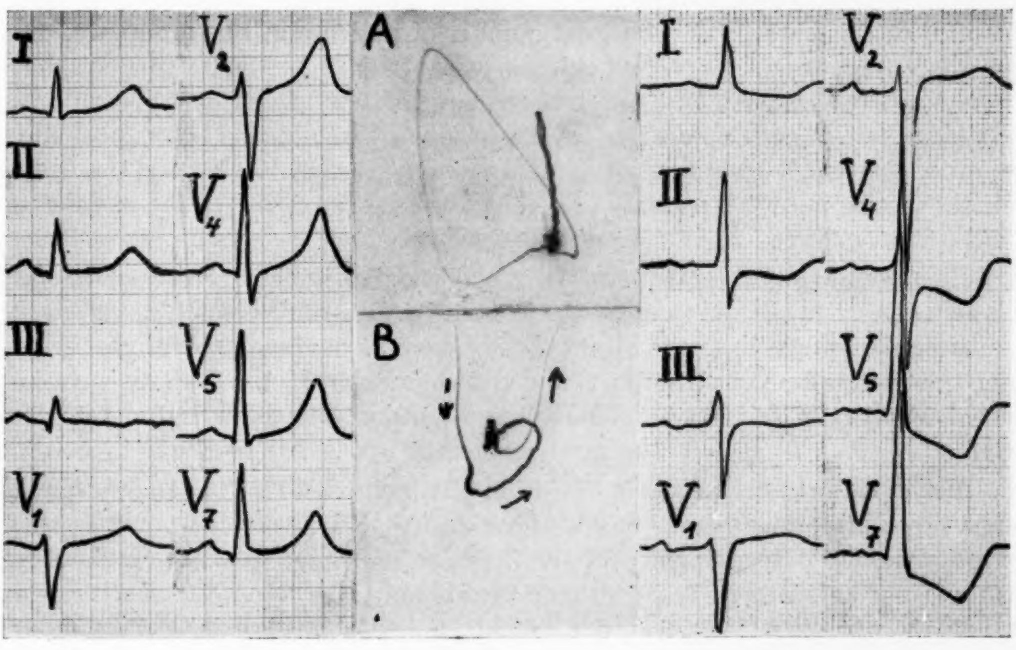

Fig. 2.—*A*, A normal horizontal plane projection of the vectorcardiogram obtained from a healthy, 32-year-old woman. The curve is composed of Leads V_1-V_5. Note the appearance of the TsÊ loop. There is a distinct long axis, because the repolarization is more nearly synchronous than in the hypertrophied left ventricular wall. *B*, Vectorcardiogram composed of the same leads as in *A*, from a case of aortic stenosis (Case 44, Table I). The short axis of the ellipsoid TsÊ loop is now 200 per cent of the original long axis because of the phase difference of the repolarization potentials. The direction of inscription of the TsÊ loop indicates the direction of the delayed potentials ($X = V_5$) ($Y = V_1$). On the left are the electrocardiographic records of the normal case, and on the right are those of the case with aortic stenosis.

B. *Aortic Valvular Disease.*—There are only 2 cases with aortic valvular disease in the present series. One of them (Case 44) was included under *Hypertensive Disease*, but because of the unilateral hypertrophy of the left ventricular wall, the case offers special interest and is included also in this group.

The second case (Case 5) showed a moderate phase difference of 45 per cent in the TsÊ loop of the sagittal plane projection, whereas in the first-mentioned

case there was a phase difference of 200 per cent in the horizontal plane projection of the TsÊ loop (Fig. 2). In both instances a potential of injury was recognizable after the completed depolarization. The electrocardiographic records were almost identical and were rather typical of left ventricular strain. The heart volumes were 500 and 470 ml./M.^{2} of body surface, respectively. In both cases the increase in the roentgenologic heart volume was merely slight, it is true, but the enlarged left ventricle alone was responsible for the increased heart volume. Moreover, such circumstances as increased systolic work of the left ventricle, due to the stenosed aortic ostium, and electrocardiographic signs of stress of the left ventricular wall are arguments for localized hypertrophy in this part of the myocardial wall.

C. *Cardiosclerosis.*—In addition to all cases of cardiosclerosis proper, cases of general arteriosclerosis, myocardial infarction, and hypercholesterolemia were classified in this category. The total number of patients in this group was 13. The mean roentgenologic heart volume was 670 ml./M.^{2} of body surface. There was 1 case (Case 23) with a heart volume of 360 ml./M.^{2} of body surface. However, the latter displayed an acute episode of myocardial lesion, probably infarction, although such an etiology could not be proved. In 8 cases the heart volume was between 400 and 550 ml./M.^{2} of body surface, and in the remaining 4 cases it was above 550 ml./M.^{2} of body surface.

Electrocardiogram: In 3 cases there was a delay in the activation time of the ventricles. A marked Q wave was present in 3 cases, whereas 1 case showed a rather low voltage in Leads II and III. Left axis deviation was present in 4 cases. S-T elevation occurred in 1, and S-T depression in 4. T waves were inverted or diphasic in 5 cases. There were 5 normal electrocardiograms in this group.

Vectorcardiogram: Left axis deviation of the maximal vector of the frontal plane projection occurred in 7 cases. Discordant QRS-T vectors were present in 10 instances. Phase difference in the TsÊ loop was recognizable in 7 cases, representing an average heart volume of 540 ml./M.^{2} of body surface. The corresponding figure for cases with roentgenologically normal heart volume and without any phase difference in the TsÊ loop (Case 23) was 360 ml./M.^{2} of body surface. In another case (Case 29) a varying degree of phase difference was observed. The variation was between 0 and 100 per cent, and the relative heart volume measured 880 ml./M.^{2} of body surface; at the same time there was atrial fibrillation and a severe heart incompensation.

The average phase shift in the TsÊ loop in cases with a heart volume between 400 and 550 ml./M.^{2} of body surface was 65 per cent. The corresponding figure for cases with roentgenologic heart volume above 550 ml./M.^{2} of body surface was 30 per cent.

D. *Various Conditions.*—This category consisted of 10 cases. Their mean roentgenologic heart volume measured 550 ml./M.^{2} of body surface. There were 7 cases with heart volumes between 400 and 550 ml./M.^{2} of body surface; in 2 of them it was above the last-mentioned figure, and in 1 case it was 330 ml./M.^{2} of body surface.

Electrocardiogram: Left axis deviation could be established in 3 cases. Depression of the S-T interval was present in 2 cases and T waves were inverted in 1. Two instances showed pre-excitation. There were, in all, 5 normal electrocardiograms in this group.

Vectorcardiogram: In 7 of 10 cases there was left axis deviation of the maximal vector of the frontal plane projection. Discordance between the QRS and T vectors was present in 4 cases. Potential of injury was manifested in 2 cases. The average heart volume in cases without any evidence of increased short axis of the TsÊ loop was 680 ml./M.^{2} of body surface. Cases with phase shift in the TsÊ loop showed a mean roentgenologic heart volume of 420 ml./M.^{2} of body surface.

DISCUSSION

The division of the material into three different groups according to the roentgenologic heart volume seemed unavoidable. Since no phase difference in the TsÊ loop was observable in any of the vectorcardiographic plane projections of normal cases, which comprised 54 healthy individuals, 25 males and 29 females, between 18 and 69 years of age, and since the TsÊ loop presented the same characteristic in cases with pronounced heart enlargement, more attention was paid to instances with only slight or moderate increase in the heart volume. It was established that a marked phase difference in the TsÊ loop was frequently combined with a rather insignificant roentgenologic enlargement of the heart. Moreover, it often occurred on both sides near the border line between the normal and pathologic heart volumes. On the other hand, the distribution of the initial, localized forms of left ventricular hypertrophy showed a rather poor correspondence as regards the roentgenologic heart volume.

The early hypertrophy of the myocardial wall as an initial response to the need of increased cardiac work is well known by pathologists. Myocardial hypertrophy, which has not been detected roentgenologically, is by no means a rare post-mortem finding. In fact, the roentgenologic estimation of the heart volume is an inadequate indicator of myocardial hypertrophy. Boyd[3] states that in the dilatation process, hypertrophy of the myocardial layer occurs as a first stage. Furthermore, it has been proved that myocardial hypertrophy of the left ventricle may exist when the roentgenologic heart volume is 450 ml./M.^{2}, or even less. In cases of initial myocardial hypertrophy, an increase of myocardial weight without volume change of the entire heart has been found post mortem.[5]

When it became obvious that initial left ventricular hypertrophy is frequently combined with normal or only slightly increased roentgenologic heart volume, the material was divided into three categories. The first, consisting of those cases with volumes below 400 ml./M.^{2} of body surface, was considered to represent absence of any myocardial hypertrophy. To the second category were allocated those cases with roentgenologic heart volumes near the upper limit, between 400 and 550 ml./M.^{2} of body surface. Initial forms of hypertrophy, often localized to some part of the left ventricular wall, were very likely to be encountered in

this group. The third category included the cases with markedly increased heart volume. Here, the hypertrophic process was generally more advanced and comprised the entire left ventricular wall. The notable enlargement of the cardiac volume was due also to the coexistent dilatation of the cavities.

Phase Difference.—The most marked phase difference in the TsÊ loop occurred in the group of cases with heart volumes between 400 and 550 ml./M.^{2} of body surface. It was observed in 19 such cases, i.e., 73 per cent of all cases of this volume group and 40 per cent of the entire series.

It has been shown that this phenomenon, which is minimal or absent in physiologic states, occurs in myocardial disease when there is a loss of electrically active elementary units, as in myocardial infarction. Here, the destruction of fibers leads to imbalance of vector integration. Some of the intact areas become manifest and contribute to the formation of new integration vectors. The entire process of repolarization shows, however, a certain disintegration, which is due to the actual repolarization potentials coming from different and mutually distant parts of the myocardium. This leads to retardation, which can be recorded vectorcardiographically as phase difference.

There is good reason for suggesting that the propagation wave of repolarization shows similar retardation in myocardial hypertrophy. Since there are repolarization potentials within a wide range, as regards time course and polarity, the recorded TsÊ loop or T wave must be considered as an integration of manifest repolarization potentials. When there is a distinctly localized hypertrophy in some part of the left ventricular wall, the time course of the repolarization potentials corresponding to this part of the myocardial wall obviously will show delay as compared with those transmitted by the intact parts of the myocardial wall. This time delay will influence the integration of the repolarization potentials from the entire myocardium by causing an increasing mutual time difference. As shown by Prinzmetal and co-workers, there is, normally, a time difference between endo- and epicardial repolarization potentials. However, normally, there is no phase difference, or only an inconsiderable one, in the TsÊ loop. The results of the present investigation, when scrutinized in the light of Prinzmetal and co-workers' reports as to the time course of repolarization, suggest that the time difference in question will increase with increasing thickness of the left ventricular wall, provided that the hypertrophy is limited to a minor part of the muscular mass. No direct estimations of this time delay have been made, however.

Consequently, the existing correlation between the increased time delay of the repolarization potential through the hypertrophied myocardial wall and the increased phase difference of the TsÊ loop has not been proved experimentally. Nor has there been any opportunity to correlate the phase difference recognizable from the TsÊ loop with autopsy findings. Since such an investigation would take an unduly long time, in that initial forms of myocardial hypertrophy are most often encountered in relatively young and healthy individuals, logical deductions are all that can be made as regards the results of the present series.

Vectorcardiographic recording offers the possibility of estimating indirectly the interrelationship of the repolarization time differences. These can be observed

not only from the usual plane projections but also from any vectorcardiographic curve composed of two arbitrarily selected electrocardiographic leads, for example, V_1-V_4 or V_1-V_5. Normally, there should be no, or only an inconsiderable, phase difference in the TsÊ loop synthetized in this manner.

In the present material, phase difference was absent not only in normal instances but also in cases with marked heart enlargement. The logical explanation for this is the multidirectional increase of repolarization time delay in the diffuse hypertrophy of the myocardium. Hence, the multidirectional retardation will lead to uniformity of the repolarization times, causing falling off of phase difference. The vectorcardiographic pattern is now similar to normal cases, with the exception of increased discordance between T and QRS axes and, sometimes, coexisting potential of injury.

Since the unilateral delay can be determined indirectly by recording repolarization potentials simultaneously on two different coordinates, an electrocardiogram representing projections on a single coordinate is not adequate for its evaluation. In the introduction to this paper it has been suggested that the T wave of a single electrocardiographic lead is very unsuitable for the estimation of the repolarization process in the entire myocardium, because of the difficulty in plotting its duration. In addition, it should be noted that the more remote the electrode is, the more do extrinsic potentials complicate the summation of the manifest T wave. Actually, potentials from superficial myocardial layers alone appear in the manifest T wave.[15] In spite of this, vectorcardiographically combined ECG leads will record mutual time differences, which represent the additional information necessary for estimation of the possible existing delay of repolarization potential. Accordingly, the time delay through the most superficial layer near the epicardium is responsible for the phase difference.

Because the hypertrophy is the result of increased thickness of the myocardial fibers, and evidently also of increased number of the fibers, the basic reason for the time delay, apart from the increased interior resistance of the single hypertrophic fiber, is the increased number of conductor elements.

An examination of the foregoing results illustrates, at all events, the diagnostic significance of phase difference in hypertrophic growth of the myocardium. In each group the phase difference was most marked in heart volumes between 400 and 550 ml./M.² of body surface, i.e., when there was an initial, localized form of hypertrophy of the left ventricular wall (Fig. 3).

In Group A, comprising cases with hypertensive disease, the mean value of the heart volume of instances with phase difference or repolarization potential was 520 ml./M.² of body surface, and that of the remaining cases without any phase shift was 730 ml./M.² of body surface.

In Group B, one of the 2 cases of aortic valvular disease with a heart volume of 500 ml./M.² of body surface showed a phase difference in the TsÊ loop of approximately 200 per cent. This case (Case 44) is of special interest because the moderate increase in the heart volume could be shown even roentgenologically as being due mainly to left ventricular enlargement. It would hardly be a mistake to assume the presence of a coexisting myocardial hypertrophy, especially in view of the rather long-standing strain on the left ventricle.

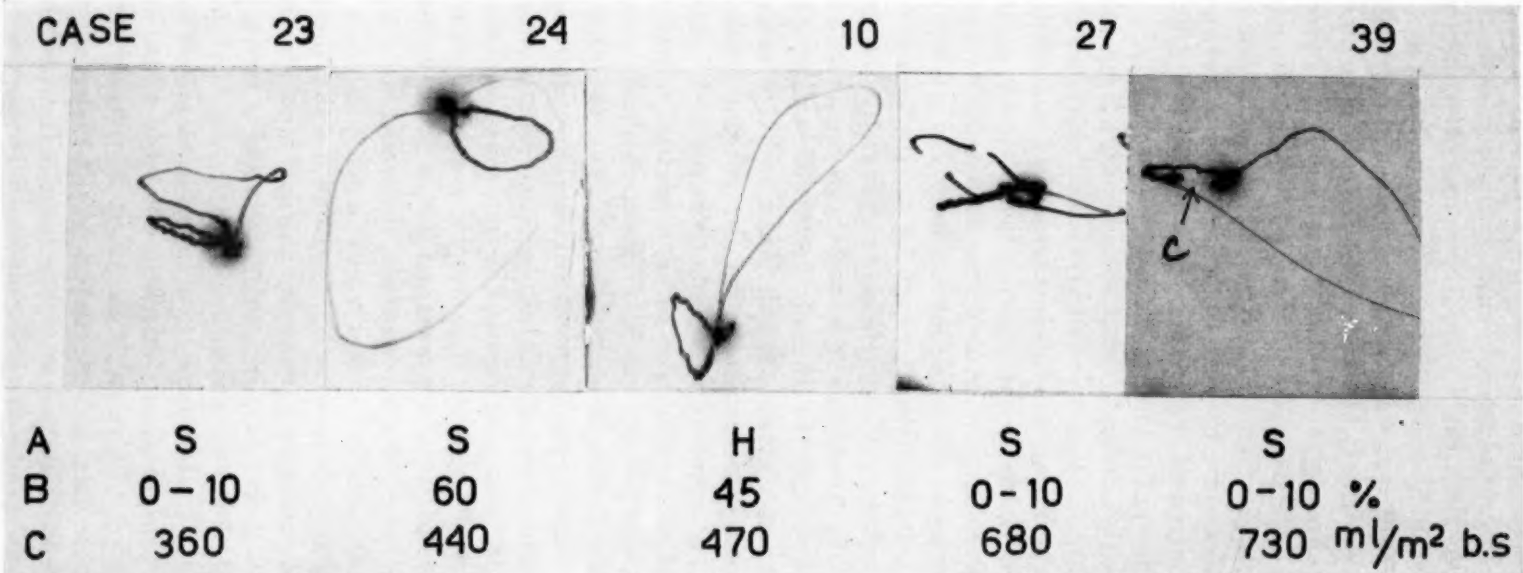

Fig. 3.—Some selected vectorcardiographic plane projections from the present series. There is a marked phase difference in the TsÊ loop in Cases 24 and 10, representing only slight increase in the roentgenologic heart volumes of 440 and 470 ml./M.^{2} of body surface, respectively. No phase difference is to be observed in Case 23 with roentgenologic heart volume of 360 ml./M.^{2}, nor in Cases 27 and 39 with marked heart enlargement. In Case 39 there is, besides a discordance between the maximal vectors of the QRSsÊ and TsÊ loops, a noticeable potential of injury (*C*). *A*, Projection plane. *B*, Degree of phase difference. *C*, The roentgenologic heart volume.

As regards the cases of cardiosclerosis in Group C, including myocardial infarction, arteriosclerosis, and hypercholesterolemia without pathologic elevation of the blood pressure, the results are not so distinct as in the other diagnostic groups, although fully explicable. The mean heart volume in 7 cases showing phase difference in the TsÊ loop was 540 ml./M.^{2} of body surface; the corresponding figure of the entire series in question was 670 ml./M.^{2} of body surface. There was, however, no significant difference when the first-mentioned figure was compared with the mean heart volume of the cases having heart enlargement but no phase difference in the TsÊ loop. It is to be noted that the cases are too few and not representative enough for this diagnostic category. In many instances there has been a long-standing anoxic process in the heart muscle, leading to advanced and diffuse changes with subsequent reparative fibrosis and extensive nonlocalized compensatory hypertrophy.

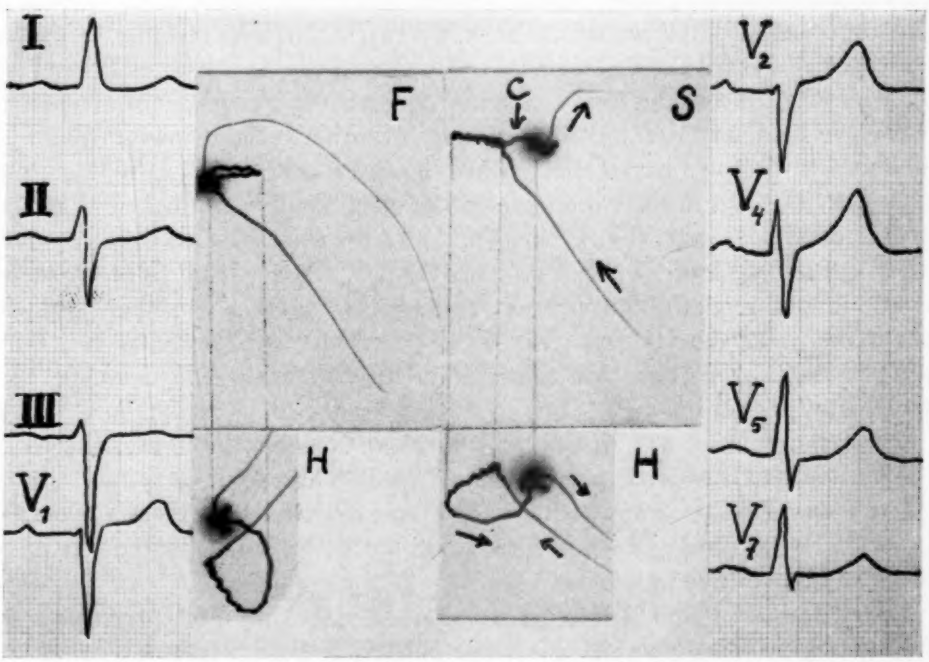

Fig. 4.—Phase difference recognizable from the TsÊ loop of Case 42 (Table I). The phase difference can be observed from the horizontal plane projection only, because the loop is most parallel with this plane. The frontal plane projection is seemingly normal. From the sagittal plane projection a rather marked potential of injury can be seen, which leaves the TsÊ loop unclosed (*C*). - Phase difference is about 80 per cent. This instance showed normal electrocardiographic tracings (left and right) and a roentgenologic heart volume of 440 ml./M.^{2} of body surface. Clinically, there was anginal pain of effort type, myocardial infarction once, and hypercholesterolemia.

An additional deleterious factor affecting the judging of the results is myocardial infarction. This condition has been established clinically in 4 cases, but obviously has been present in others as well. Usually, a healed myocardial infarction does not leave any phase difference in the TsÊ loop (Case 23), unless there is a subsequent myocardial hypertrophy (Case 10), in which event the shape

and size of the TsÊ loop show a notable stability. In acute lesion, as in myocardial infarction, the instability in shape and size of the TsÊ loop is a remarkable feature. This is the most important vectorcardiographic differential diagnostic criterion between these two conditions.

In 10 cases representing various clinical conditions—Group D—there was again good correspondence between the distribution of cases with phase difference in the TsÊ loop and that of roentgenologic heart volumes. The average heart volume in cases showing phase difference in the TsÊ loop was 420 ml./M.^{2} of body surface, whereas the corresponding volume in cases without any phase difference was 680 ml./M.^{2} of body surface. Also in the present group there was excellent reciprocity between the vectorcardiographic conclusions of existing left ventricular hypertrophy and the actual clinical findings.

In reviewing the electrocardiographic results, some remarks must be made regarding the diagnosis of left ventricular hypertrophy. There were altogether 13 normal electrocardiograms. Among these there was only 1 case without any clinical or roentgenologic evidence of left ventricular hypertrophy (Case 35). One of them (Case 46) showed a phase difference in the TsÊ loop of 130 per cent. This patient had a long history of angina pectoris, and there were at least two clinically verified myocardial infarctions. Another case showing poor correspondence with the normal electrocardiogram was Case 42 (Fig. 4). Here, as in the previous case, hypercholesterolemia and clinically established myocardial infarction were revealed on one occasion. There was a phase difference of 80 per cent in the TsÊ loop of the vectorcardiogram. Apart from hypercholesterolemia and an old myocardial infarction, there was an arterial hypertension, which supports the view that left ventricular hypertrophy was present. In the remaining cases as well there was clinical and/or roentgenologic evidence of left ventricular hypertrophy.

Left axis deviation was encountered in 20 instances. Two cases showed left axis deviation as an isolated phenomenon (Cases 6 and 42).

There was a delayed activation time of the ventricles in 3 cases and LBBB in 2 cases. High voltage in leads corresponding to the left ventricle was present in one, and low voltage in another case.

S-T suppression and T-wave inversion in extremity and precordial leads corresponding to the left ventricle were encountered in 9 cases. In 10 other instances S-T suppression occurred solely in a pair of the extremity leads and/or one or more precordial leads over the left ventricle. T-wave inversion or diphasity in the above leads was found in 8 cases. S-T suppression together with T-wave inversion in precordial leads corresponding to the left ventricle are regarded as the most reliable electrocardiographic criteria of hypertrophy of the left ventricular wall. These changes are thought to be produced by the repolarization time delay in the hypertrophied part of the left ventricular wall.[6]

In general, it may be said that the electrocardiographic findings of the present series were not unequivocal. They showed rather bad reciprocity with the vectorcardiographic results. This applied especially to the suppression of the S-T interval and to the inversion of the T wave, which may show similar changes in anoxemic conditions.

CONCLUSIONS AND SUMMARY

1. Forty-seven cases were analyzed in respect to their roentgenologic heart volumes and vectorcardiographic phase differences recognizable from the TsÊ loop. The material was divided into three groups; the first consisted of cases with roentgenologic heart volume below 400 ml./M.^{2} of body surface, the second of cases between 400 and 550 ml./M.^{2} of body surface, and the third of cases above 550 ml./M.^{2}.

2. When the material was classified as to the degree of phase difference in the TsÊ loop, it was found that the most marked phase difference occurred in cases with heart volume between 400 and 550 ml./M.^{2} of body surface, i.e., near the normal limit. Hearts with normal volume, as well as with more advanced cardiac dilatation, did not show any marked phase shift in the TsÊ loop.

3. The phenomenon of phase difference in the TsÊ loop has been interpreted in accordance with the results obtained by Prinzmetal and co-workers as to the characteristics of the repolarization potential of the heart muscle.

4. The phase difference is caused by the time delay of the repolarization potential through the unilateral myocardial hypertrophy. In normal cases this time delay is minimal or absent, causing the normal TsÊ loop with its predominating and distinct long axis. In advanced hypertrophy and dilatation there will be a multidirectional delay of the repolarization waves, again causing loss of the phase difference. There are now, however, other vectorcardiographic criteria of myocardial disease, such as increased discordance between the QRS and T vectors and, in addition, an occasional coexistent potential of injury.

5. Thirteen cases had normal electrocardiograms. In 2 of these cases, in which the histories included hypercholesterolemia and clinically verified myocardial infarctions, the phase difference was very much accentuated. The heart volumes were at the normal upper limit.

6. In a case with aortic stenosis the slightly increased heart volume was caused by the markedly enlarged left ventricle. Here, the phase difference was 200 per cent when the increased short axis of the TsÊ loop was compared with its long axis.

7. The phase difference of the TsÊ loop, which makes manifest the mutual time differences of the repolarization potentials, affords an indirect estimation of the heart muscle conductivity and thus shows its applicability to the diagnosis of early left ventricular hypertrophy.

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Myocarditis With Endocardial Elastomyofibrosis (EEMF)

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Varying degrees of endocardial thickening are not uncommonly observed in a variety of conditions at necropsy. In most instances this alteration is considered to be of little or no clinical significance. However, increasing interest has been demonstrated concerning an uncommon form of heart disease in which endocardial thickening of one or both ventricles, as well as myocardial fibrosis, particularly of inner muscle bundles, represent salient features. The endocardial thickening morphologically appears as collagenous connective tissue containing variable amounts of elastic fibers. Affected hearts, in the vast majority of instances, are hypertrophied and/or dilated. Outstanding is the failure to demonstrate the usual causal factors, viz., significant coronary atherosclerosis, primary valvular disease, hypertension, or bronchopulmonary disease. Mural thrombi are frequent, although the incidence of embolic phenomena has been considered less than might be expected from the frequency of the former. The pericardium is uninvolved, and aside from the case of Fienberg and Holzman,[1] which exhibited a pyramidal mass of myocardium projecting into the right ventricle, and a case recorded by Bedford and Konstam,[2] in which hypoplasia of the aorta was present, congenital anomalies have not been observed. Similarly, systemic alterations which might be related to the cardiac lesions have not been demonstrated conclusively, although Becker and associates[3] considered alterations in the former to indicate that the disorder was a type of "collagen disease." Stemmermann[4] recently called attention to the association of such a cardiac lesion and pancreatitis, but considered the latter to represent, most likely, a manifestation of "stress."

There appears to be a predisposition to this disorder in young adults previously considered to be in good health; many cases have been reported among military personnel. However, examples in both sexes in later decades as well as in adolescents have been well documented. The outstanding clinical manifestations appear related to cardiac failure, which may pursue a relatively short course or one which is more protracted and remittent. If both ventricular cavities are involved, the features simulate those of constrictive pericarditis. Indeed, thoracotomy has been performed on at least two occasions because of such a mistaken clinical diagnosis.[5,6] The pathologic physiology with impaired diastolic-

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filling and systolic ejection appears similar in both conditions, and the results of recent catheterization studies of the right ventricle in an example of this disorder were similar in all respects to those observed in constrictive pericarditis.[6] Cardiac murmurs are inconstant and appear, at least in part, to be dependent upon extension of the endocardial process to the valve leaflets. Electrocardiographic findings are nonspecific, revealing a variety of T-wave and QRS changes. Anginal pain is uncommon, and fever is usually absent unless bronchopneumonia or other septic complication intervenes. Eosinophilia, although a variable feature, may be of diagnostic value. A hypochromic anemia may be observed.

Reports of examples of heart disease with many of the anatomic and clinical features outlined above have appeared under various appellations. Most of these emphasize certain morphologic characteristics (e.g., endocarditis fibroplastica parietalis,[7] endomyocardial fibrosis[8]), or its obscure or idiopathic nature. The term "endomyocardial fibrosis" has gained recent popularity, largely through the excellent anatomic studies by Davies and associates[8,9] of examples of this type of heart disease. However, the results of our study of such a case, as well as the findings in 109 consecutive, unselected hearts at necropsy, indicate that hypertrophy of endocardial smooth muscle as well as elastic fibers constitute outstanding features of the endocardial thickening.[10] Therefore, we consider the descriptive term "endocardial elastomyofibrosis" (EEMF) more appropriate. In addition to the varied nomenclature employed, nosological confusion has arisen from the peculiar geographical distribution of reported cases. Although we have not had the opportunity to personally examine the hearts from the various areas from which such reports have emanated, the excellent documentation allows for an analysis which warrants the conclusion that the cases observed in various parts of Africa[8,9,11-15] (including the cases of Becker and associates[3] from the southern portion of that continent), and those reported in Switzerland,[7,16-18] Germany,[19] Austria,[20] France,[21,22] Australia,[23] England,[24,25] and the United States,[1,5,6,26-35] reveal sufficient similarities to be considered as a singular group. This identity, based largely on anatomic features, does not imply a common etiology, but may be of conceptual value regarding the pathogenesis of these cardiac alterations. Whether those examples of unexplained cardiac hypertrophy with relatively little or no endocardial change recorded by Evans,[36] or the cases of Higginson and associates,[37] represent a separate entity or, perhaps, a stage in the process accounting for EEMF cannot be answered at this time. On the other hand, those examples of heart disease considered as representing an adult form of so-called congenital fibroelastosis, recently reported by Thomas and associates[38] and others,[39] appear to exhibit anatomic features allowing for their distinction from EEMF, a view also held by others. However, some of the cases[40-42] recorded with such an interpretation appear to belong more clearly in that group of heart disease which we have designated as EEMF. Significant anatomic differences as well as clinical features allow for its distinction from somewhat similar cardiac alterations observed in scleroderma or beriberi.

Recently, we have encountered an instance of heart disease in a 23-year-old white male Korean veteran which had all of the classical features of examples of EEMF referred to above. In addition, eosinophilia was an outstanding clinical

feature, thus making it identical in all respects to those cases recorded by Löffler,[7] in 1936, as endocarditis fibroplastica parietalis, and by others.[1,6,25] However, unlike other previous examples of EEMF, the coronary arteries revealed almost complete luminal occlusion due to atherosclerosis. In addition, an incomplete defect of the muscular portion of the interventricular septum was present. This report is concerned with the presentation of the clinical and pathologic findings in this patient which allow for certain comments relative to etiology and pathogenesis. This case has also prompted our review of the examples of endocardial thickening observed in 109 unselected, consecutive necropsies, in an attempt to gain some insight into possible mechanisms associated with this alteration. The results of the latter study form the basis of another report.[10]

CASE REPORT

The patient, a 23-year-old white man, first noticed burning, postprandial epigastric pain, scotomata, headache, and subungual hemorrhages while serving in the Army in Korea. He had no significant past medical history. One sibling had been rejected from military service because of a "heart murmur." Laboratory studies revealed a leukocytosis of 20,000 with 60 per cent eosinophils, and an elevated sedimentation rate. Ancylostoma and Ascaris ova were identified by stool examination. He was treated with hexylresorcinol and tetrachlorethylene, which resulted in relief from the gastrointestinal symptoms. However, the eosinophilia persisted. Blood cultures, lupus erythematosus preparations, heterophil antibody test, and tuberculin test (PPD first and second strengths) were negative. A muscle biopsy failed to reveal significant pathologic alteration. A Trichinella skin test was positive on one occasion, but a subsequent complement fixation test was reported as negative. He experienced a slight elevation of temperature to 100°F. during his illness, but did not have chills. An ECG (Fig.1) revealed changes considered suggestive of pericarditis, but x-ray examination of the chest was not considered abnormal (Fig. 2). Although he had no complaints or signs referable to the cardiovascular system, he was placed on complete bed rest. He was transferred to another hospital 8 weeks after the onset of his illness.

Examination at that time revealed the point of maximal impulse to be 1 cm. to the left of the mid-clavicular line. The heart tones were somewhat distant but of good quality. The rhythm was regular and no murmurs or rubs were audible. The blood pressure was 128/70 mm. Hg, and the pulse 100 per minute. The difference between brachial and femoral pressures was not unusual. He continued to display a leukocytosis of 10,000 to 15,000 per c.mm. with 40 per cent eosinophils and low-grade fever. A moderate anemia of 3.9 million erythrocytes and 11.5 Gm. of hemoglobin became evident. Urinalyses, serologic tests for syphilis, sedimentation rates, stool examination, liver and kidney function tests were considered within normal limits. Electrocardiograms were interpreted as revealing left heart strain in a vertical heart. No specific therapy was instituted, and the patient continued to be apparently free from cardiovascular symptoms. However, he subsequently developed tachycardia of 120 per minute, gallop rhythm, precordial tightness, and exertional dyspnea. Chest x-rays showed a cardiothoracic ratio of 48 per cent, and fluoroscopy was considered compatible but not diagnostic of pericardial effusion. He was transferred to another hospital approximately 10 weeks following his second hospitalization. Examination revealed full neck veins. Recent and old retinal hemorrhages were also evident but papilledema was absent. The heart was noted to pulsate vigorously to the left of the mid-clavicular line. A Grade 2 systolic murmur was heard at the apex, with transmission to the left axilla. Blood pressure was 120/80 mm. Hg. The liver edge was palpable 5 cm. beneath the right costal margin and was moderately tender. Although edema was not demonstrable, a weight loss of 10 pounds followed the administration of a mercurial diuretic. Blood cultures were negative. Urinalyses revealed varying amounts of protein, specific gravities of 1.018 or less, and varying numbers of casts. Electrocardiograms were considered abnormal but of no specific diagnostic pattern. He was treated with diuretics, digitalis, and quinidine, with moderate effectiveness. Cortisone was also administered and resulted in marked subjective improvement and decrease of eosinophils to normal

values, and some decrease in heart size. Stool examination on one later occasion revealed ova of Ancylostoma and Ascaris, but subsequent examinations following antihelminthic therapy were negative. Eosinophilia present at that time also subsided with this treatment. He was referred to another hospital for further observation after 2 months.

At this time the patient complained of dyspnea, weakness, and epigastric pain. Electrocardiograms revealed atrial premature contractions, right axis deviation, and T-ST changes due to digitalis and sinus tachycardia. Withdrawal of cortisone was followed by the signs and symptoms of extreme heart failure. There was tachycardia, low pulse pressure, and a mitral systolic murmur as noted previously. The heart tones were considered good, however, and cardiac pulsation was not considered abnormal by fluoroscopy. Examination several weeks later revealed the pulse to be 110 per minute; the blood pressure was 92/90 (?) mm. Hg. A prominent precordial heave was noted and the point of maximal impulse was in the sixth left intercostal space between the mid-clavicular and anterior axillary lines. The systolic murmur noted previously was heard,

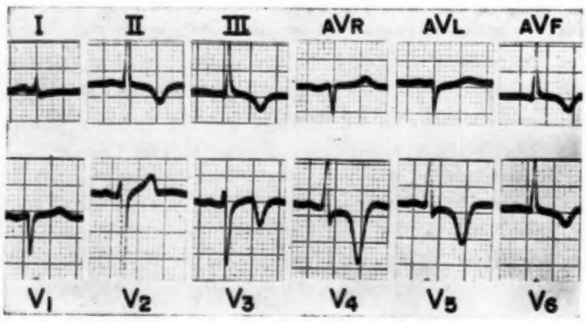

Fig. 1.—First ECG showing nonspecific T and S-T abnormalities.

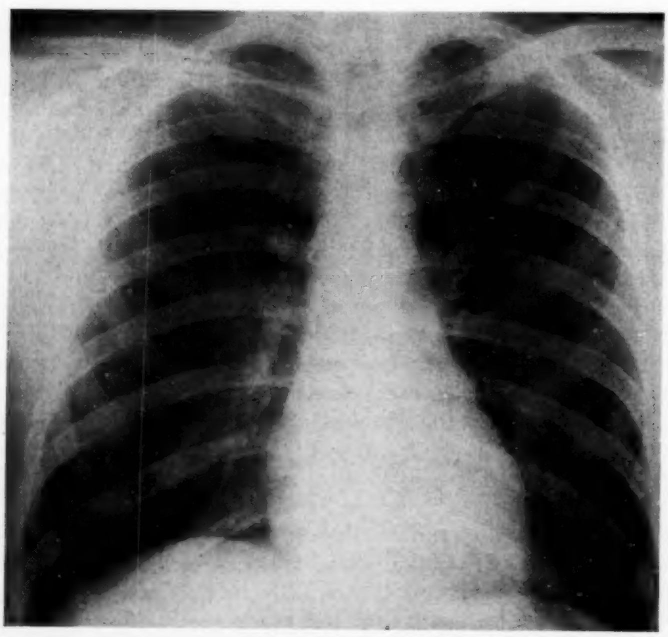

Fig. 2.—Normal-appearing roentgenogram of the chest in earlier part of illness.

and the pulmonic second sound was considered greater than the aortic second sound. A protodiastolic gallop was also evident. Ascites and pretibial edema were apparent. Cardiac enlargement with fullness of the pulmonary artery and questionable dilatation of the right atrium was noted by x-ray. Electrocardiograms revealed right axis deviation and digitalis effect (Fig. 3) and, subsequently, atrial fibrillation. Laboratory examination revealed white blood cells averaging 15,000 per c.mm. with only 1 per cent eosinophils. Urinalyses were negative except that the specific gravities never exceeded 1.010. The nonprotein nitrogen was 36 mg. per cent.

The patient failed to respond to diuretics, digitalis, and supportive measures. Several weeks prior to death he experienced hemoptysis associated with pain and tenderness in the left foot. X-ray of the chest revealed general cardiac enlargement (Fig. 4). Bilateral superficial venous femoral ligation was performed. However, this failed to alter the ingravescent course, and the patient succumbed approximately 1 year following the onset of his illness.

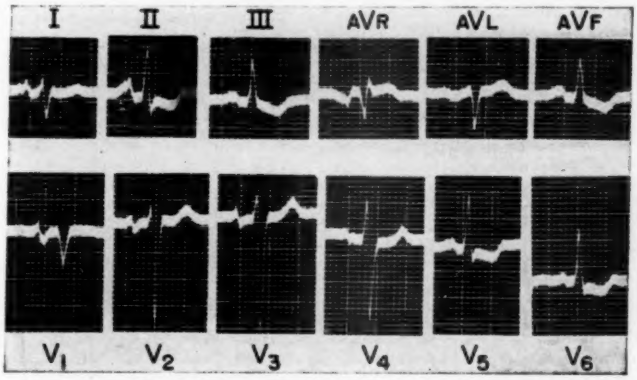

Fig. 3.—ECG with nonspecific changes different from those noted earlier (Fig. 1).

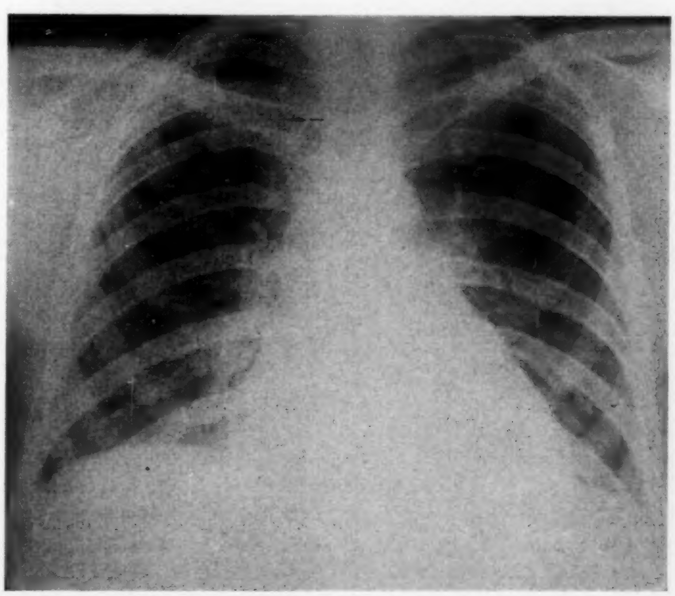

Fig. 4.—Roentgenogram of the chest prior to death, showing marked cardiac enlargement and pulmonary congestion.

NECROPSY

Gross Findings.—The body was well developed and weighed approximately 150 pounds. Marked edema of the lower extremities and scrotum was present. Petechiae were evident in the skin of the chest and upper extremities. Approximately 1,500 c.c. of clear, yellow fluid was present in both pleural cavities, and 100 c.c. in the pericardial sac.

The combined weight of the lungs was 875 grams. They were moderately firm. Their cut surfaces were congested but relatively dry. A recent infarct measuring 2 by 2 cm. was present in the right middle lobe.

Fig. 5.—Endocardium of left ventricle is rugose, thickened. Papillary muscles are indistinct.

The heart weighed 385 grams. The pericardial and epicardial surfaces were, for the most part, smooth and glistening. A few petechiae and small fibrous plaques were present in the epicardium. The left ventricle measured 1.7 cm. at its thickest portion, and the right 0.7 cm. The myocardium was reddish-brown and homogeneous, except in the septum, where fine, interlacing foci of fibrosis were apparent. The entire endocardial surface of the inflow tract of the left ventricle, including the inferior two thirds of this chamber, was thickened, measuring 0.5 cm. at its thickest area (Fig. 5). The most caudad portion appeared greenish-grey and rugose, and its surface was friable (fibrin thrombus), whereas this thickening was less irregular and more distinctly white at its superior margin. The papillary muscles were not clearly evident in the area of endocardial thickening, and the base of several chordae tendineae which were involved in the process were thickened and fused. The mitral and aortic valves, measuring 11 and 7 cm., respectively, were grossly normal. The entire circumference of the inflow tract of the right ventricle was also thickened by a grey-white plaque (Fig. 6). Its surface was slightly furrowed but lacked the superficial deposits of fibrin observed in the left ventricle. A circular defect measuring 2 cm. in diameter was observed in the muscular portion of the interventricular septum of the right ventricle above the area of endocardial thickening. It extended into the septal musculature for a

distance of 1 cm. Its lining was smooth and there was no apparent herniation into the left ventricle. The tricuspid and pulmonic valves appeared normal, measuring 12 and 7 cm., respectively. The foramen ovale was anatomically closed. Marked luminal narrowing due to atherosclerosis, and approximating 80 per cent compensation, was focally evident in both coronary arteries 1 cm. from their origin. The coronary ostia were not remarkable and the aorta revealed only focal minimal atherosclerotic change.

The liver, which weighed 2,000 grams, spleen, and kidneys revealed congestion; the former assumed the classical nutmeg appearance.

Microscopic Findings.—Thirty-five sections of heart, including atria, valves, and grossly involved and uninvolved portions of both ventricles, were stained with hematoxylin and eosin, Verhoeff-van Gieson technique for elastic fibers, smooth muscle and collagen, and the phosphotungstic acid hematoxylin (P.T.A.H.) method. Aside from a rare focus of lymphocytes, the epicardium was not remarkable. Myocardial fibers in all chambers appeared larger than usual and many contained rectangular nuclei. Myocytolysis, intra- and intercellular edema were apparent, particularly in myocardial fibers disposed in proximity to the lumen of the chamber. Focal interstitial myocardial fibrosis was apparent in many areas, particularly about vessels (Fig. 7).

Fig. 6.—The endocardial surface of inflow portion of the right ventricle is thickened. A probe is in the muscular septal defect.

Although myocardial fibrosis was severe beneath the endocardium, a preserved layer of cardiac muscle between the zone of endocardial alteration and the former was occasionally encountered. Interstitial collections of eosinophils (Fig. 8) and, rarely, lymphocytes were not infrequent. Aside from the degenerative changes cited, there was no evidence of active myocardial necrosis. The endocardial surfaces of the atria were thickened, being comprised of increased numbers of elastic fibers arranged in an orderly pattern parallel to the luminal surfaces. Relatively little collagen was evident among these fibers. The appearance of the endocardium in the ventricles was varied. Sections from the left ventricle from that area which grossly contained mural thrombus exhibited an outer layer of fibrin subtended by relatively acellular collagenous connective tissue containing moderate numbers of delicate endothelial-lined channels, macrophages containing hemosiderin, as well as hemofuscin and scattered lymphocytes (Fig. 9). Beneath this zone an intact layer of elastic fibers could be discerned above either intact or fibrotic musculature. In some areas

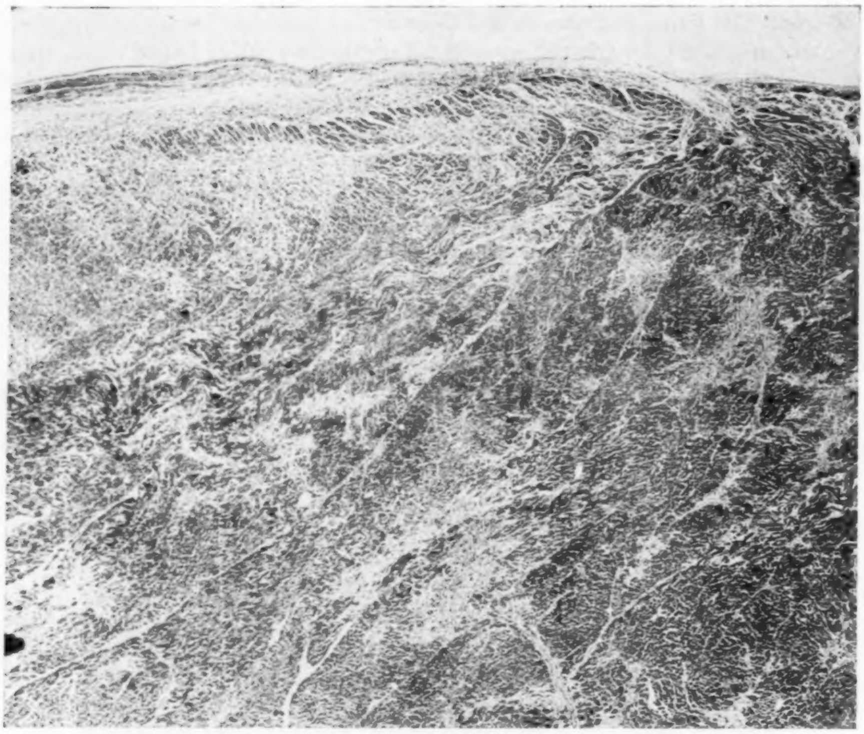

Fig. 7.—Pale areas of focal myocardial fibrosis. (P.T.A.H. Magnification, × 15; reduced ½.)

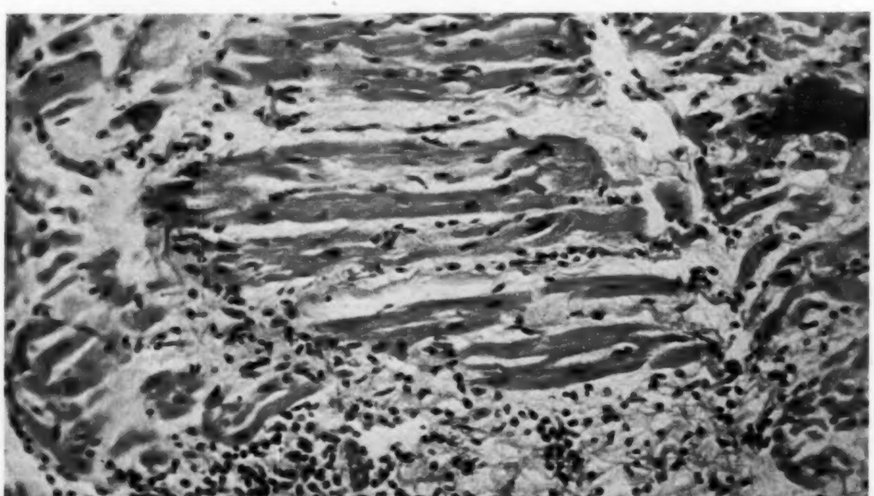

Fig. 8.—Interstitial inflammatory infiltrate comprised principally of eosinophils. (Magnification, × 185; reduced ½.)

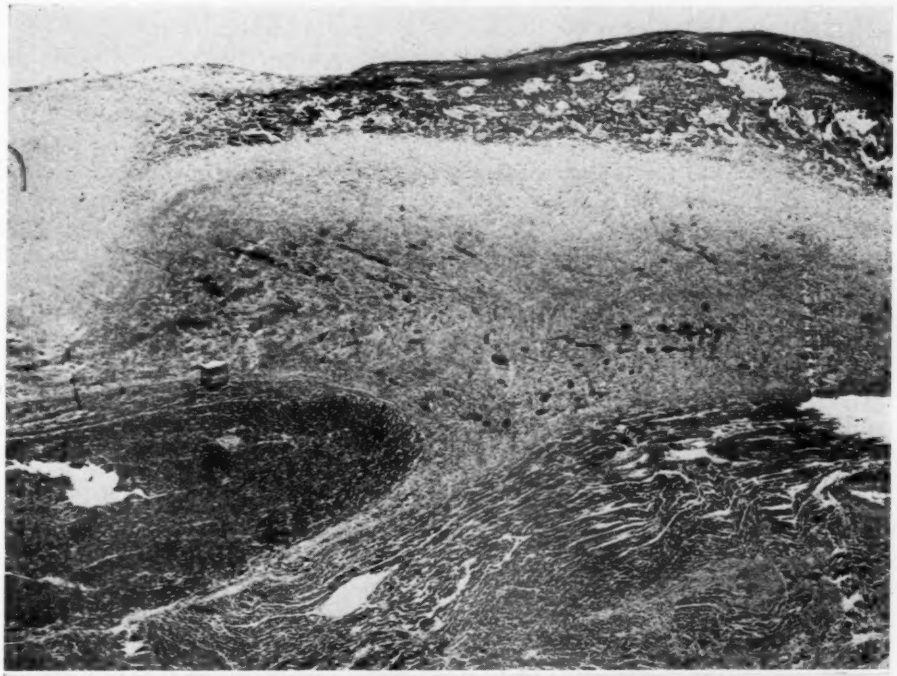

Fig. 9.

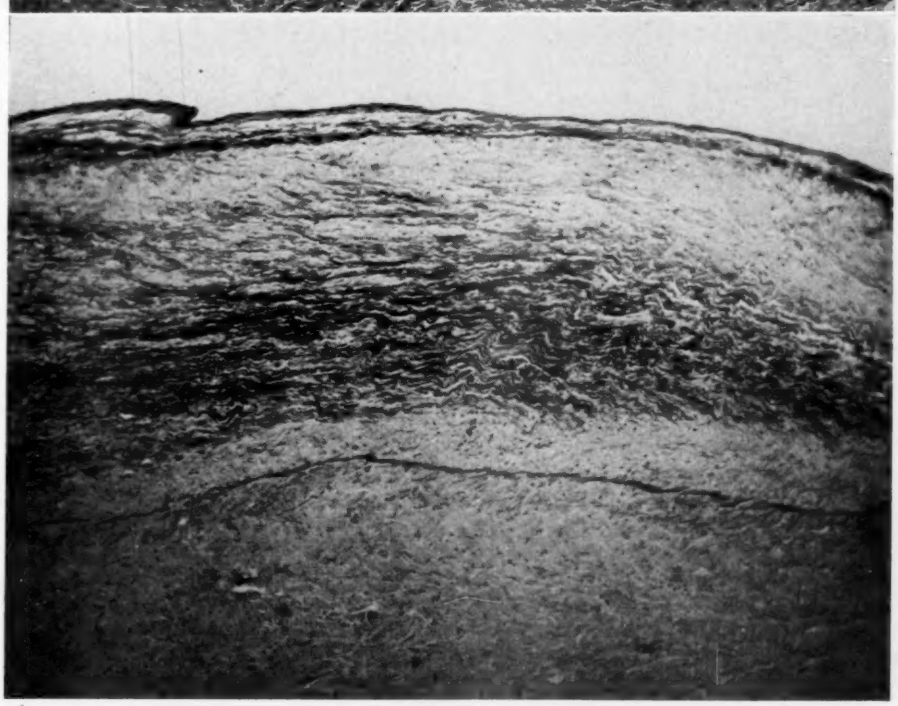

Fig. 10.

Fig. 9.—Section at inflow tract of left ventricle, revealing superficial fibrinous layer (appearing black) subtended by collagen and numerous dilated vascular channels. (P.T.A.H. Magnification, × 15; reduced ⅙.)

Fig. 10.—Section of left ventricle adjacent to mural thrombus, revealing elastic tissue hyperplasia: Some cells in the pale staining areas contain features of smooth muscle. (Verhoeff-van Gieson. Magnification, × 95; reduced ⅙.)

tongue-like projections of the endocardial thickening extended into the myocardium for varying distances. Elastic hyperplasia was not infrequently evident in such areas, and whorls of hyperplastic fibers were noted about isolated bundles of cardiac muscle. Sections observed from the focus of endocardial thickening in the right ventricle as well as the superior portion of that noted in the left revealed much elastic tissue hyperplasia arranged in an orderly pattern parallel to the lumina of these chambers (Fig. 10). A distinct layer of smooth muscle could be discerned separating hyperplastic elastic fibers in the endocardium in some of the sections, and remnants of smooth muscle, as evidenced by myoglial fibers in sections stained by the P.T.A.H. method, were evident in zones revealing almost exclusive collagenization. Sections of myocardium about the interventricular septal defect appeared similar to that noted above. Its endocardial layer revealed moderate elastic tissue hyperplasia. Many myocardial arterioles exhibited thickened walls, and in some, organized and recanalized thrombi were evident. Acute vasculitis was not apparent. Sections of valves revealed nonvascularized normal structures. No parasites were observed within the many sections studied.

Fig. 11.—Cross section of anterior descending coronary artery demonstrating luminal narrowing due to atherosclerotic plaque. (Magnification, × 20.)

Sections of the coronary arteries revealed the lumina to be eccentric due to marked intimal fibrosis and collections of foam cells and cholesterol clefts (Fig. 11). Elastic tissue stains failed to reveal any unusual perivascular elastic hyperplasia in the major coronary arteries or their intramyocardial ramifications.

No anatomic findings which might be interpreted as evidence of a systemic disease of connective tissue or its components, including elastic fibers, were disclosed in other viscera. The liver revealed severe hemorrhagic central necrosis with inversion of hepatic lobular architecture. Moderate numbers of hemosiderin-laden macrophages were present in the alveoli of the lungs. There was hyperplasia of the bone marrow, principally granulocytic, and congestion of spleen and kidneys. Moderate lipid depletion of the adrenal cortices was present. Sections of diaphragm revealed rare foci of necrosis but parasites were not identified.

COMMENT

The clinical manifestations exhibited by the patient of this report epitomize those observed in other examples of this unusual form of heart disease. Similarly, many of the pathologic findings in the heart, notably severe endocardial thickening, principally of the inflow tracts of both ventricles, mural thrombosis, myocardial hypertrophy, and dilatation and degenerative and fibrotic myocardial changes, particularly of inner muscle bundles, are in keeping with the anatomic aspects of this disorder. In addition, interstitial inflammatory infiltration, comprised principally of eosinophils in this instance, has been noted on occasion.[1,25,29,32,41] On the other hand, the marked narrowing of the lumina of the major coronary arteries is a unique finding in this disorder. Although vasculitis such as polyarteritis nodosa has been considered as possibly being responsible for some instances of coronary arteriosclerosis in young adults,[43] the microscopic appearance of affected vessels was distinctly that of atherosclerosis, lacking the mural alterations and conspicuous periadventitial sclerosis characteristic of healed periarteritis.[44] Also, visceral and other vessels appeared unaltered. The occurrence of coronary atherosclerosis in young adults has been well documented.[45] Although endocardial thickening may occur in hearts with severe atherosclerosis, it is noteworthy that major infarction was not observed in this case. In addition, the over-all distribution of areas of myocardial fibrosis and interstitial eosinophilic infiltrate in the absence of overt myocardial necrosis are distinctly dissimilar from those changes of atherosclerotic heart disease which may simulate the alterations observed in this disorder. It is considered, therefore, that the disease of the major coronary arteries observed in this patient is etiologically unrelated to the cardiac lesions observed, although it is not unlikely that it played a role in their pathogenesis (infra vide).

Many reports of this form of heart disease have indicated the variable presence of elastic fibers in the endocardial lesion. Indeed, this characteristic has been considered one of the features differentiating this disorder from congenital fibroelastosis, in which such fibers are uniformly hyperplastic. However, it appears significant that the latter were frequently observed in the case presented, except in those areas where organization of mural thrombus was conspicuous. In addition, such fibers represented a major component of the tongue-like fibrous projections noted to extend from the endocardium into the underlying muscle. They appeared in such sites to be of greater magnitude than might be expected by a relative increase subsequent to stromal collapse. Another component of the endocardial thickening which has received little recent attention was the hypertrophy of smooth muscle fiber, particularly in the outflow tract. Although it was poorly formed in areas with the most severe endocardial thickening, such as the inflow tracts, these latter revealed frequent cells with the morphologic and tinctorial features of smooth muscle. It is likely that these muscular elements are derived from smooth muscle, which has been considered to form an integral part of the normal endocardium, although in our own studies of normal hearts such structures are sparse. Recently, Haust and More[46] have called attention to the presence of cells, with the morphologic features of smooth muscle cells, which have assumed a fibroblastic function in the intima of vessels

undergoing organization of thrombi. They considered the possibility that such cells reflect the need for contractile elements in a thickened, relatively inert area. It is of interest that both hypertrophy of smooth muscle and the proliferation of elastic fibers represent conspicuous features of varying degrees of endocardial thickening which is commonly observed at necropsy.[10] Their pathogenetic implications will be discussed subsequently. No changes which might be interpreted as indicative of a so-called collagen or other systemic disease were encountered in the heart or other tissues of the patient presented. Although the mild pancreatitis observed may be due to "stress," as suggested by Stemmermann,[4] it appears equally tenable that it is related to the administration of cortisone in this patient.[47]

The pathogenesis and etiology of the cardiac alterations in this disorder have not been completely elucidated. It is commonly held that the endocardial change is due, in part, to organization of mural thrombus secondary to the myocardial damage. The adverse effect of endocardial fibrosis on the function of the arterioluminal and thebesian vessels is then visualized as perpetuating a vicious cycle of myocardial and endocardial alterations. The markedly dilated capillary channels noted in the areas of endomyocardial damage have been interpreted as reflecting such a disturbance in these accessory coronary channels. The studies of Wearn,[48] concerning the directional flow in the arterioluminal vessels under conditions of increased pressure in the right ventricle, which may be present in these cases, are compatible with such an assumption. However, the directional flow of the arterioluminal vessels in the left ventricle is unknown. The recognition of some preserved subendocardial fibers in the presence of severe atherosclerosis in this case would suggest that the function of these vessels was not significantly impaired. Another explanation concerning the pathogenesis of the endocardial changes noted is suggested by the recent analysis of examples of congenital fibroelastosis by Black-Schaffer.[49] He has revived some earlier proposals that have emphasized the relationship of such endocardial change to hypertrophy and dilatation. These latter conditions increase myocardial tension proportional to the cube of the radius, according to Laplace's law ($T \propto R^3$), rather than in a direct manner, a situation obviously not favorable for cardiac function. The elastosis encountered is considered to represent an attempt of the structure to restore more normal myocardial tension, according to Hooke's law ($T \propto R^2$). Since the change is not purely one of proliferation of elastic tissue, this compensatory development obviously falls short of full effectiveness. Proliferation of elastic fibers as well as hypertrophy of smooth muscle are well-recognized alterations in vessels subjected to increased tension, e.g., the interlobular arteries in accelerated hypertension. A certain degree of collagenization may also be observed under this circumstance, and an apparent increase of ground substance in such vessels is often conspicuous.[50] This latter change may also occur in the endocardium and therefore is not necessarily evidence of a collagen disease. In such a scheme of events mural thrombosis might occur as a result of altered hemodynamics, as observed in other cardiac chambers (e.g., auricles) in the absence of morphologic evidence of myocardial and/or endocardial damage. This mechanical concept possesses considerable merit and is worthy of further

consideration. It should be noted, however, that it does not appear applicable to all instances of cardiac dilatation and hypertrophy, since endocardial thickening may be conspicuously lacking in some examples of the latter despite the fact that the duration of heart disease may be similar to that observed in examples of EEMF. Furthermore, although heart weight appears to be directly related to severe forms of endocardial thickening, no similar relationship is evident in milder forms of this alteration.[10] Such information suggests that hypertrophy and dilatation may aggravate or augment endocardial thickening but are not exclusively responsible for its development. It would appear that both mechanisms outlined may play a role in the development of endocardial thickening, as observed in these cases. Both are complementary in that they emphasize the significance of myocardial weakness or damage leading to these alterations, the endocardial change representing a secondary phenomenon. The effect of severe coronary atherosclerosis, as noted in the patient reported, in augmenting the former needs no further elaboration. The tendency of severe endocardial alteration to occur in the inflow tracts of this and other examples of this form of heart disease appears to be related to the frequency of thrombosis at these sites.

The possibility of diversified etiologies producing such an anatomic picture has been emphasized,[25] and the myocardial changes have been related to isolated myocarditis,[5,29,30,33,35,42] allergy,[25] poor nutrition,[28] and toxic agents such as arsphenamine.[13] The presence of interstitial collections of eosinophils and, to a lesser degree, other inflammatory cells and obliterative changes in small branches of the coronary arteries in the heart of the case reported warrants a diagnosis of myocarditis. The presence of healed lesions is also compatible with this interpretation. Although the patient exhibited some of the clinical manifestations of Trichinella infestation, a well-recognized cause of myocarditis, and although a positive skin test for this disease was obtained, absolute diagnosis of Trichinella infestation cannot be made in this instance. The negative complement fixation test and the presence of other parasites which may give a cross reaction to Trichinella skin antigen[51] militate against such a diagnosis. Parasites could not be identified in sections of diaphragm, although only a few blocks of this structure were examined. However, the possibility that the myocarditis was related to the hookworm infestation assumes importance when it is appreciated that myocarditis has been observed, albeit rarely, in association with this condition.[52] It is of interest to note that cardiac damage has also been observed following the administration of hexylresorcinol.[53,54] Indeed, its administration has been considered contraindicated in persons with heart disease.[53] Tetrachlorethylene, which this patient also received, on the other hand, has no known cardiotoxic effect.[54] Although the existence of parasitic myocarditis has not been conclusively demonstrated, at best a difficult task, nevertheless, its possible etiological significance, for reasons cited, cannot be entirely dismissed. It is germane to note in this regard that eosinophilia is a common feature of the African cases of EEMF, which constitute the vast majority of examples of this disorder.[8,9] This finding has been attributed to the frequent parasitic infestation of Africans, although no comments relative to the possible etiological relationship of such infestation to the myocardial changes have been made. It is also of interest that the other

examples of EEMF associated with eosinophilia observed in this country[1,6,26] have been in servicemen or veterans who were stationed in the South Pacific, a locale well recognized for its prevalence of parasitic infestation. Two of these had malaria. This does not imply that all or even most examples of this disorder are the result of parasitic myocarditis, for other etiologies, as noted above, also appear tenable. It does indicate, however, that such agents may play a significant etiological role in this disorder, particularly in those cases with eosinophilia.

The predominate outflow involvement, relative lack of myocardial changes, infrequent thrombotic phenomena, and elastic tissue nature of the endocardial thickening have been emphasized as distinguishing anatomic features of the hearts in congenital fibroelastosis observed in infants as well as adults and in EEMF.[25,38] It is apparent, however, that if the congenital form persists into adulthood, subsequent involvement with myocarditis or other alteration may not only precipitate cardiac failure but also alter the appearance of the heart to resemble that observed in EEMF. This contention is compatible with the pathologic findings noted in the case of this report. Unfortunately, we have been unable to obtain information concerning the nature of the heart disease of this patient's sibling which prompted his exemption from military service. The occurrence of congenital fibroelastosis in siblings is well recognized but has not been recorded in examples of EEMF. Moreover, the presence of congenital defects in the congenital form of fibroelastosis is frequent. The septal defect encountered in this patient appears to represent such an anomaly. These considerations suggest that a relationship between the congenital form of fibroelastosis and this disorder may exist. However, it still remains to be demonstrated whether such severe endocardial involvement is capable of existing into adulthood without symptoms, particularly in individuals participating in vigorous activity.

The association of variable degrees of endocardial thickening in such rare forms of heart disease as beriberi, or in persons with progressive systemic sclerosis, is well recognized. Aside from their apparent etiology such hearts usually present anatomic differences sufficient to distinguish them from the disorder described in this report. The myocardial fibrosis in progressive systemic sclerosis rarely circumscribes vessels and often appears to be more fibroblastic than that observed in EEMF. Also, endocardial fibrosis is often slight or negligible.[55] This also tends to occur in beriberi which, in addition, exhibits predominant right ventricular involvement, more conspicuous myocytolysis, and less myocardial fibrosis.[52]

Therefore, it is considered that although endocardial thickening may be observed in a variety of conditions, the type referred to in the above discussion as endocardial elastomyofibrosis (EEMF) associated with myocarditis represents a distinct clinical group with similar anatomic features. The pathogenesis of the endocardial thickening may be reparative as well as mechanical. Both concepts emphasize the primacy of myocardial involvement. It is considered highly tenable that in the case presented this was due to a myocarditis of parasitic origin. The possibility that the myocarditis was superimposed upon a congenital form of fibroelastosis persisting into adulthood is theoretically plausible. However, the majority of instances of heart disease considered as representing adult forms of congenital fibroelastosis possess pathologic features distinctive from those

of myocarditis with EEMF. The nosological position of those examples of markedly hypertrophied hearts without endocardial thickening or significant myocardial alteration and obscure etiology is also uncertain at present.

SUMMARY

An example of cardiac failure due to myocarditis associated with severe endocardial elastomyofibrosis, in a 23-year-old white man, is presented. The clinical course and anatomic features closely parallel those described in that form of heart disease most frequently, but not exclusively, observed in Africa and designated as endomyocardial fibrosis, Löffler's endocarditis fibroplastica parietalis, etc. In addition, severe atherosclerosis of the coronary arteries was present. This latter condition is considered pathogenetically but not etiologically related to the cardiac alterations encountered.

The patient's clinical history, infestation with Ascaris, Ancylostoma, and possibly Trichinella, as well as the demonstration of blood eosinophilia and an eosinophilic myocarditis, are considered strongly suggestive of the parasitic nature of the myocarditis, despite the failure to demonstrate such organisms within the heart. Although it is recognized that this type of heart disease may have various etiologies, it is proposed that parasitic myocarditis may be more frequent in this regard than was previously appreciated, particularly in those instances with eosinophilia.

The primacy of myocardial damage in producing the endocardial alteration observed is emphasized and the latter is attributed to both reparative as well as mechanical phenomena.

The relationship of this apparently singular group of rare cardiac disorders to some recorded instances of idiopathic cardiomegaly and adult forms of so-called congenital fibroelastosis remains to be demonstrated.

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Observations Concerning the Pathogenesis of Endocardial Thickening in the Adult Heart

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Clinical and pathologic interest has been revived concerning the lesion commonly designated as endocardial sclerosis. This has resulted largely from the recent attention to an unusual form of adult heart disease characterized by a severe cardiac failure which may pursue either a relatively short course or one that is more protracted and remittent, but nevertheless progressive. One of its salient pathologic features is marked endocardial thickening. Its nosological relationship to congenital fibroelastosis and instances of obscure cardiac hypertrophy in which endocardial thickening is minimal or absent is at present uncertain. In the previous report[1] an example of this form of heart disease was described in detail, and the possible mechanisms which might be involved in the pathogenesis of the endocardial lesion were discussed. In the light of our findings the interpretation was proposed that the latter may be the result of both reparative and mechanical factors dependent upon myocardial damage or weakness. It was considered worthwhile, therefore, to analyze the forms of endocardial thickening commonly encountered at necropsy in a variety of conditions, with the hope of gaining further insight into some of the factors which may play a role in the pathogenesis of this change.

MATERIAL AND METHODS

The hearts from 109 consecutive, unselected autopsies were carefully examined. All were from males whose ages ranged from 26 to 90 years, with an average of 59 years. The hearts were weighed after removal of the extracardiac tissue and the aorta above the aortic valve. The valves were measured in the usual manner, and the thickness of the ventricular myocardium was estimated at its widest portion, excluding the papillary muscles. The degree of endocardial sclerosis was arbitrarily classified as: none (0), mild (+), moderate (2+), or severe (3+). The distribution of this change, whether diffuse, inflow or outflow, was also indicated. The degree of coronary atherosclerosis was estimated from that portion of the vessel revealing the most severe degree of luminal occlusion. Vessels considered as having Grade 1 atherosclerosis revealed less than 25 per cent luminal occlusion; Grade 2, 25 to 50 per cent; Grade 3, 50 to 75 per cent; and Grade 4, 75 per cent or more.

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Blocks from each heart were taken from both atria, including the atrioventricular valves and the posterior wall of the inflow and outflow tracts, the latter just beneath the semilunar valves, as well as from other areas revealing endocardial thickening or other abnormality. All tissue was fixed in Formalin, and the sections were prepared in the usual manner and stained with hematoxylin and eosin and the Verhoeff-van Gieson technique for elastica, smooth muscle, and collagen. Sections from the coronary arteries were similarly prepared. Selected sections of the heart were also stained by the phosphotungstic acid hematoxylin technique.

RESULTS

Incidence and Site of Endocardial Thickening.—Of the hearts examined, 39.5 per cent failed to reveal any degree of endocardial thickening macroscopically.

Fig. 1.—Heart with endocardial thickening located principally in the outflow tract of the left ventricle. The endocardial sclerosis is considered severe or 3+.

It was considered mild in 33.9 per cent, moderate in 21.1 per cent, and severe in only 5.5 per cent (Table I; Fig. 1). Endocardial thickening was 6 times more frequent in the left than in the right ventricle, only 11 per cent of the cases revealing this change in the latter. The few cases of right ventricular thickening do not permit any statement relative to a particular location of this change in this chamber. However, it is apparent from Table II that mild endocardial thickening of the left ventricle is found almost exclusively in the outflow tract, whereas moderate and severe degrees were observed to be equally diffusely distributed throughout the ventricle as well as only in the outflow tract.

Nature of Endocardial Thickening.—It readily became apparent from microscopic study of sections stained by the Verhoeff-van Gieson technique that the

endocardial thickening observed macroscopically was comprised not only of relatively acellular collagen but also of a proliferation of elastic fibers which were most often oriented parallel to the lumen. Not infrequently the elastic fibers comprised the bulk of the endocardial thickening and were observed in that portion of the endocardium corresponding to the parietal layer. An almost constant finding in sections of thickened endocardium prepared from the outflow tract of the left ventricle was a well-defined band of smooth muscle interposed between elastic fibers adjacent to the lumen (Fig. 2). These findings have prompted us to designate this type of endocardial thickening as "endocardial elastomyofibrosis" (EEMF). Another band of elastic fibers accompanied by fibrous tissue was present in the visceral zone of the endocardium. Occasionally, dilated capillary channels were observed within the latter area. On the other hand, areas of endocardial thickening which covered zones of myocardial fibrosis were comprised almost exclusively of fibrous tissue, appearing most severe in the presence of recognizable fibrin thrombus (Fig. 3). In none of the hearts were myocardial changes observed which might be interpreted as indicative of recent or remote myocarditis. Areas of myocardial fibrosis could be correlated with the severity of the disease of the major coronary arteries, which appeared in all instances to be of the atherosclerotic type.

Relationship of EEMF to Age.—There was apparently no significant relationship between the average age or range of ages of the patients and the degree of endocardial thickening observed (Table I).

TABLE I. INCIDENCE OF EEMF AND RELATIONSHIP TO HEART WEIGHT AND AGE

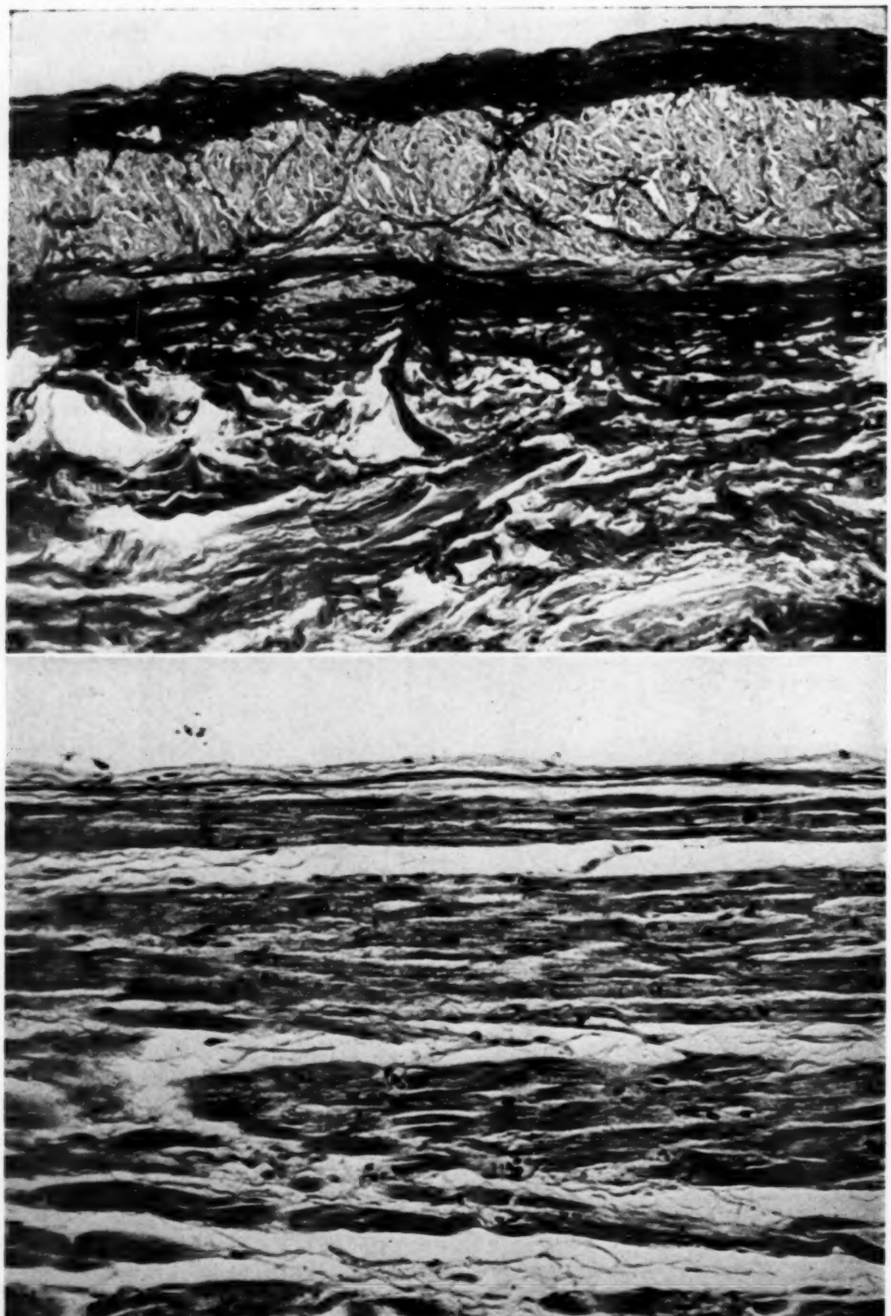
DEGREE OF EEMF	NUMBER	AVERAGE AGE (YR.)	AVERAGE HEART WEIGHT	PER CENT
0	43	55	363 ± 80	39.5
1+	37	59	358 ± 81	33.9
2+	23	62	358 ± 100	21.1
3+	6	57	520 ± 73	5.5

Groups	*Significance (P Value)*
0, 1+, 2+ and 3+	<0.05
0 and 1+, 2+	>0.1

TABLE II. RELATIONSHIP OF DEGREE OF EEMF TO LOCATION

DEGREE OF EEMF	OUTFLOW (%)	INFLOW (%)	DIFFUSE (%)
1+	92.5	0	7.5
2+	52	4	43
3+	50	0	50

A.



B.

Fig. 2.—*A*, Severe endocardial thickening characterized by hyperplasia of elastica and hypertrophied smooth muscle (magnification, × 240), as compared with *B*, a section from same area of heart without macroscopic evidence of endocardial change (magnification, × 215). (*A* and *B*, Verhoeff-van Gieson stain; both reduced ⅙.)

Relationship of EEMF to Heart Weight.—As noted in Table I the weight of the hearts* in those instances in which severe endocardial thickening was observed was statistically greater than that in hearts in which milder forms of this endocardial change were encountered. Similarly, more severe EEMF was noted in those hearts revealing dilatation as evidenced by the circumference of the tricuspid and mitral valves being greater than 12.5 and 9.5 cm., respectively (Table III). There was no apparent relationship between the degree of EEMF and valvular measurements which appeared significantly less than those cited.

Fig. 3.—Reparative endocardial fibrosis in papillary muscle. There is only a scant amount of endocardial elastica present. (Verhoeff-van Gieson. Magnification, × 70; reduced ⅛.)

Relationship of EEMF to Grade of Coronary Atherosclerosis.—Table III indicates that severe EEMF was approximately twice as likely to occur in a heart in which severe coronary atherosclerosis (Grade 4) was present. However, the converse, i.e., that severe coronary atherosclerosis was directly related to marked EEMF, was not obtained. It is of interest that the weight of the hearts in persons with severe atherosclerosis was statistically greater than that in hearts with milder forms of coronary change, regardless of the presence or absence of EEMF. Twelve of the hearts examined revealed evidence of myocardial infarction; in 11 of them the condition was remote. Only 17 per cent of these revealed severe EEMF, whereas 50 per cent were without this change. There was no statistically significant difference in the weight of these latter hearts regardless of the presence or absence of endocardial thickening.

*It is appreciated that a more exact expression of cardiac weight is that based on body weight. Unfortunately, the latter was not indicated in all protocols received.

TABLE III. RELATIONSHIP OF SEVERITY OF CORONARY ATHEROSCLEROSIS AND DILATATION TO DEGREE OF EEMF

GRADE OF CORONARY ATHEROSCLEROSIS	NUMBER	DEGREE OF EEMF		
		0 to 1+	2+	3+
1	51	80%	14%	6%
2	29	72%	24%	4%
3	16	56%	44%	0%
4	13	69%	15%	16%
Dilatation:				
Left ventricle		7.5%	9%	17%
Right ventricle		10%	9%	33%

Relationship of EEMF to Various Diseases.—Unfortunately, many of the clinical protocols contained insufficient blood pressure determinations to allow for any correlation between this important factor and EEMF. However, no consistent relationship between EEMF and moderate and severe arteriolar nephrosclerosis was observed. Three of the hearts revealed frank evidence of rheumatic heart disease, viz., mitral stenosis and/or Aschoff bodies. EEMF was considered severe in only 1 heart. Similarly, no consistent relationship between EEMF and chronic pulmonary disease and/or cor pulmonale could be discerned. No one disease seemed to occur with any particular frequency in instances of severe EEMF. On the other hand, myocardial hypertrophy, on the basis of coronary atherosclerosis, hypertension, severe anemia, valvular heart disease, or severe bronchopulmonary disease, could be accounted for in all instances of this study.

COMMENT

It is generally appreciated that endocardial thickening may result from various causes. These have been classically considered to be functional or nonfunctional in nature. Factors considered as indicative of the former are the response to dilatation and hypertrophy,[2] prolonged hypertension,[3] "irritation" of blood flow,[4,5] and a reaction analogous to intimal sclerosis.[6] The extension of inflammatory processes from valvular or myocardial disease,[2,3] primary inflammation of the endocardium, and organization of mural thrombus have been considered as nonfunctional etiologies.[3] The presence of endocardial thickening in relationship to major myocardial infarction needs little elaboration. The reaction appears distinctly reparative, being comprised of relatively acellular collagen, and exhibits the features of organizing thrombus when the latter is present. Elastic tissue is notably sparse or absent, in keeping with the well-recognized failure of such connective tissue elements to proliferate in healing wounds.[7] As noted in this study, endocardial thickening is not an invariable response to myocardial infarction, appearing, in large part, to depend upon the proximity of damaged muscle to the endocardium and/or mural thrombosis. Similarly,

miliary infarcts of the myocardium may be unattended by endocardial thickening, although this phenomenon may be present if the heart is hypertrophied or dilated. In the latter instance the endocardial change has been observed to be qualitatively different from that attributed to reparative fibrosis, being comprised of proliferation of elastic tissue and hypertrophy of smooth muscle with only moderate amounts of collagen. Recognition of these components has prompted our use of the term "endocardial elastomyofibrosis" (EEMF). The presence of these structures may be accounted for on the basis of increased myocardial tension resulting from dilatation and hypertrophy, as discussed in detail in the previous report.[1]

Although the results of this study indicate a relationship between endocardial thickening and myocardial dilatation and hypertrophy, it appears significant that a direct relationship between these anatomic alterations is evident only in severe forms of endocardial thickening. In addition, some hypertrophied hearts failed to reveal endocardial thickening. It is apparent, however, that if those hearts exhibiting mild or moderate degrees of endocardial thickening at necropsy were previously dilated, a more direct relationship between this change and dilatation might be postulated, excluding those instances due to reparative change. Unfortunately, such information is not easily obtained. If, on the other hand, such is not the case, we are compelled to consider hypertrophy and dilatation as factors augmenting the endocardial process but not directly responsible for its occurrence. The almost exclusive location of mild degrees of endocardial thickening in the outflow tract suggests the possibility that one factor in this regard may be the trauma of ejected blood, since this site receives the major impact of the systolic thrust. The observed proliferation of elastic tissue might then be considered analogous to that observed in the distal limb of a coarcted aorta, a "jet" lesion, as described by Edward and associates.[8] Another factor worthy of consideration in explaining the predominately outflow location of endocardial thickening is that it is the outflow portion of the endocardium which normally possesses the most smooth muscle and elastic fibers,[4] elements which constitute a conspicuous morphologic component of endocardial thickening at this site. One might cogently inquire whether "nature" had a purpose for such an anatomic arrangement. It appears logical to assume, therefore, that the area possessing the greatest amount of responsive structures should manifest change earlier and more conspicuously than zones in which such components are sparse. Such a premise is in keeping with other previously noted considerations which emphasize the compensatory nature of this type of endocardial thickening. Also, coincident with such a hypothesis is the recognition that diffuse endocardial involvement was observed only when the endocardial thickening was considered severe. Therefore, endocardial thickening does not appear to reflect defective structure but a compensatory phenomenon. The inflow tract, long considered inherently weak, only rarely shows such a change. Severe examples at this site appear related to the organization of mural thrombus and are most frequently reparative in type.

Other factors which might be considered responsible for the initiation of endocardial thickening were not apparent. Evidence of inflammation within

the endocardium or subjacent myocardium was conspicuously absent. As indicated previously, the presence of elastic tissue within the areas of endocardial thickening argues against such an etiological concept. Although the incidence of severe endocardial thickening was noted to be approximately twice as frequent in hearts with severe coronary atherosclerosis as in those in which the latter was less marked, there does not appear to be any statistical evidence that the converse, i.e., that severe atherosclerosis of the coronary arteries is directly related to severe endocardial thickening, is true. It appears significant to note that the weight of the hearts in those instances of severe coronary atherosclerosis was significantly greater than that in hearts in which less severe forms of this vascular change were noted. This information is considered to indicate that it is the hypertrophy and dilatation resulting from myocardial ischemia, a well-recognized event, which is significant in regards to endocardial thickening rather than the coronary insufficiency per se.

It is of interest to note that it is the outflow tracts which are most severely involved in the congenital form of endocardial thickening, commonly referred to as congenital fibroelastosis. It is not within the scope of this presentation to discuss the various concepts proposed concerning the pathogenesis of the fibroelastic thickening in this disorder. It appears sufficient to note that in this form of heart disease the pathogenetic significance of mechanical factors, notably cardiac hypertrophy and dilatation, has been advanced recently by Black-Schaffer.[9] The possibility of the congenital form of endocardial thickening persisting into adulthood still remains a moot problem. Its resolution appears dependent upon the final elucidation of all factors concerned with the lesion's pathogenesis. The recognition, in this study, of diseases frequently associated with endocardial thickening would, with our present knowledge, preclude statements relating the endocardial thickening observed to the presistence of a congenital lesion into adulthood, notwithstanding the possibility that such an event may occur rarely.

SUMMARY

Necropsy examination revealed varying degrees of endocardial thickening in approximately 60 per cent of 109 consecutive, unselected hearts. In 5.5 per cent of the total it was considered severe. Microscopic examination allowed for the distinction of two types of this endocardial change. The type which is considered as reparative was characterized by fibrosis with little or no proliferation of elastic tissue or smooth muscle. It was encountered most frequently in association with major and minor myocardial infarction and the organization of mural thrombus. The compensatory or mechanical type appears as a hypertrophy of smooth muscle and hyperplasia of endocardial elastica (EEMF). Severe degrees appeared more closely related to cardiac hypertrophy and dilatation than to age or other factors investigated.

EEMF was most frequently observed in the outflow tract of the left ventricle; severe forms were observed with equal frequency at this site, as well as throughout this chamber. Since there was little indication that mild degrees of EEMF were related to cardiac hypertrophy and dilatation, it is suggested that the latter

may only accentuate this phenomenon. Other factors such as the anatomic structure of the inflow tract and the "trauma" of ejected systolic blood appear tenable as factors in this regard.

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Dissociation With Interference Between Pacemakers Located Within the A-V Conducting System

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Dissociation with interference can occur between two foci in any part of the heart. This fact was presented clearly in a recent paper on the subject, in which all the previously described possibilities, as well as the hypothetical ones, were considered. Yet, simultaneous dissociated action of two pacemakers within the A-V conducting system seems to be a rare phenomenon in view of the few clinical reports which have been published.[1-3] This refers specifically to instances in which a complete A-V block does not exist. In 1913, Meakins[4] produced A-V nodal rhythm by cooling the sinus node. Following this maneuver, a clamp, which he had invented, was applied to the A-V conducting system, using the necessary pressure to produce a complete interruption of orthograde conduction. Since the ventricular pacemaker was located before the bifurcation, both foci were situated, beyond a doubt, within the A-V junction, the atria beating faster than the ventricles.

This paper does not deal with cases of that kind, but rather with tracings in which the ventricles showed an independent activity, always with a slightly faster rate than that of the auricles. The theoretical existence of such an arrhythmia occurring in specific cardiac tissue was emphasized in the early thirties by Wachstein[5] and by Goldenberg and Rothberger,[6] who made observations concerning the interference of two or more rhythms, and of interpolated extrasystoles in isolated Purkinje fibers. Goldenberg, Gottdenker and Rothberger[7] also performed similar experiments when studying the effect of rhythmical condenser discharges on the activity and spontaneous automatism of one or various centers located in the same kind of fibers. The clinical counterpart of these disorders of rhythm in the A-V conducting system will be presented in this communication.

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CASE REPORTS

CASE 1.—The tracings presented in Figs. 1, 2, and 3 are from a 67-year-old hospitalized patient with arteriosclerotic heart disease and congestive heart failure. Fig. 1 was recorded 24 hours after initial digitalization with 2 mg. of acetyldigitoxin (administered orally in two doses). Inverted P waves are present in Lead II, as well as in Leads III and aV_F (not shown), so that it is assumed that the pacemaker which is responsible for the atrial activation is located at the uppermost region of the A-V junction. It discharges at a rate of 79 beats per minute. The ventricular complexes, having a faster rate (100 per mintue), are identical to the ones observed during sinus rhythm, so that this pacemaker is situated somewhere before the bifurcation of the common bundle. It is to be noted that the auricular and ventricular actions are regular and independent, with the P waves falling in various parts of the shorter ventricular cycles, indicating a faster beating of the ventricles. This is the most prominent characteristic of dissociation with interference. In these tracings, orthograde conduction is not present, most probably because of the normal refractoriness provoked by the lower pacemaker. Yet, some degree of A-V block must also exist in Fig. 1 so as to account for the failure of transmission of early impulses (such as the ninth atrial complex) which would otherwise be conducted to the ventricles. Some minutes before this strip (Fig. 1) was recorded, the patient had received 0.75 mg. of acetyldigitoxin, because from auscultation it had been estimated that "the sinus rate was still a little faster than desired."

The two continuous records presented in Fig. 2 were obtained 24 hours later. In the upper strip the electrocardiographic appearance is that of a ventricular tachycardia with apparently normal and independent sinus rhythm. The ventricular rate (91 per minute) is faster than the atrial. However, the true mechanism is revealed in the lower tracing. It can be seen that the atrial deflections have maintained the same rate throughout both records (86 per minute), and that the P waves are negative whenever they can be clearly outlined, falling in various parts of the shorter ventricular cycles. These characteristics allow the assumption that this pacemaker is located at the uppermost region of the A-V junction. Inspection of the strip after the fifth P wave shows a picture similar to that of Fig. 1, but at a slightly different rate.

As in all examples of dissociation with interference, the upper stimuli cannot reach the ventricles on account of the refractoriness provoked by the lower pacemaker.[8] In spite of this fact, the fifth atrial impulse penetrates farther down through the A-V conducting system than do any of the preceding ones, being stopped nevertheless before activating the ventricles. This penetration is of sufficient magnitude to discharge the lower pre-existing pacemaker, which, although located below the bifurcation, is undoubtedly reached by the impulse coming from above. Since its effect is revealed only by the unexpected failure of appearance of the following beat from the same pacemaker, this finding can be considered as an example of concealed A-V conduction, a term introduced by Langendorf.[9] Following this phenomenon, the next ventricular contraction originates before the bifurcation at a rate of 97 per minute, evidence of which is the normal contour of the QRS complexes, similar to the ones seen during interference beats (Fig. 3). Subsequently, dissociation persists, as stated before, similarly as in Fig. 1.

Fig. 3 was obtained two days after Fig. 2, in spite of no further administration of digitalis. In this tracing the atria are under the control of the sinus node, which discharges at a slightly irregular rate, ranging from 97 to 107 per minute, obviously faster than the rate of the upper A-V nodal rhythm observed in Figs. 1 and 2. The positive P waves are clearly outlined throughout the record. At the beginning of the tracing, an A-V dissociation is present, with the A-V pacemaker located before the bifurcation, and with a faster rate (125 per minute) than the sinus rhythm.

It can be observed that the third atrial impulse has a deeper penetration through the A-V junction than any of the preceding ones, for it reaches the automatic center, depressing it slightly, before being stopped shortly thereafter. This manifestation represents the usual form of concealed conduction, as stated in the diagram. Consequently, the next (fifth) ventricular complex originates in another region (at a rate of 115 per minute), farther down the A-V conducting system, probably below the bifurcation. This assumption is favored by the existence of the abnormal morphology of the QRS complexes. The lower pacemaker controls the ventricles during three beats, but only until the occurrence of the sixth atrial impulse, which has a deeper penetration

through the A-V conducting system than do any of the preceding ones (including P_3). This greater degree of penetration is of sufficient magnitude to discharge the lower automatic center, but not great enough to activate the ventricles. No ventricular action is seen during the interval (1.08 second) which follows the seventh QRS complex, so that this pause ends with a conducted beat from the atria. Thus, this finding is in contrast with what takes place after the first instance in

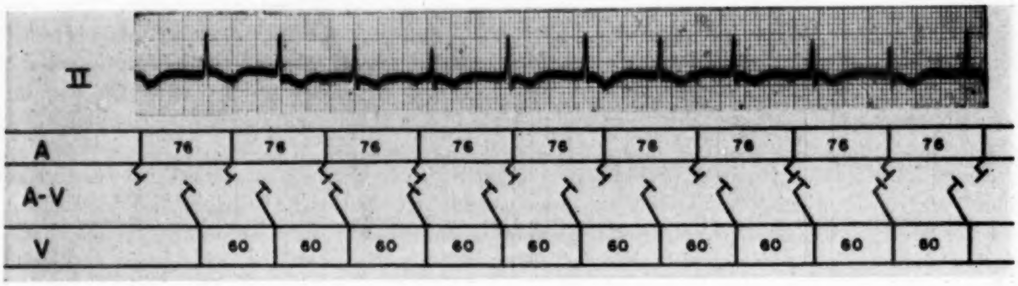

Fig. 1.—Dissociation with interference between pacemakers located, one at the uppermost region of the A-V conducting system, and the other, before the bifurcation of the common bundle. Because of the high rates of both centers, this tracing can be considered also as an instance of simultaneous, independent, nonparoxysmal A-V tachycardias. Diagrams are conventional.[9] (For discussion see text.)

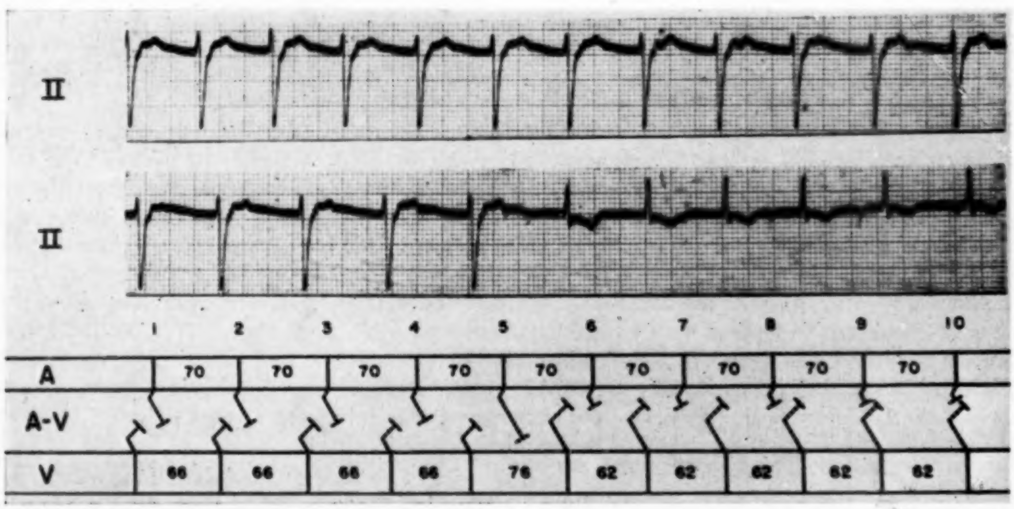

Fig. 2.—Dissociation with interference between pacemakers located, one at the uppermost region of the A-V conducting system, and the other, alternatively after and before the bifurcation. Because of the high rates of both centers, these tracings can also be considered as examples of simultaneous A-V tachycardias. The two strips are continuous. (For discussion see text.)

which concealed conduction was produced (P_3), for at that time another automatic beat appeared before a conducted sinus impulse had enough time to reach the ventricles. Moreover, on the second occasion, not only one, but two conducted beats are observed, both with a prolonged P-R interval, which indicates some degree of A-V block (0.24 second). Subsequently, A-V dissociation is re-established, with the same characteristics as those observed on the initial part of the strip. One day later the records of this patient showed sinus rhythm with a prolonged P-R interval (0.22 second), which gradually returned to the accepted normal limits.

CASE 2.—The electrocardiograms presented in Fig. 4 were obtained from a 74-year-old patient with arteriosclerotic heart disease and congestive heart failure. He had been receiving 0.75 mg. of digoxin daily for the previous two months. The tracing was obtained at the request of the attending physician, because of the fact that auscultation had revealed "sinus bradycardia interrupted by intermittent extrasystoles." It shows inverted P waves in Leads II and III, so that

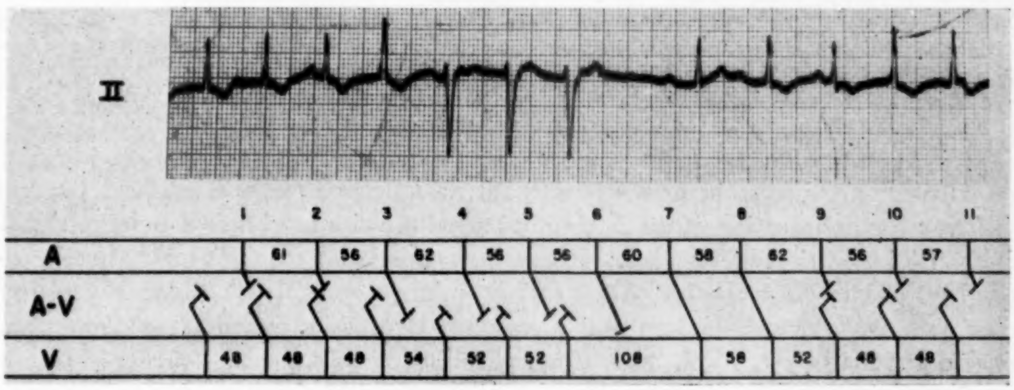

Fig. 3.—Dissociation with interference between pacemakers located, one at the sinus node, and the other, alternatively before and after the bifurcation of the common bundle. (For discussion see text.)

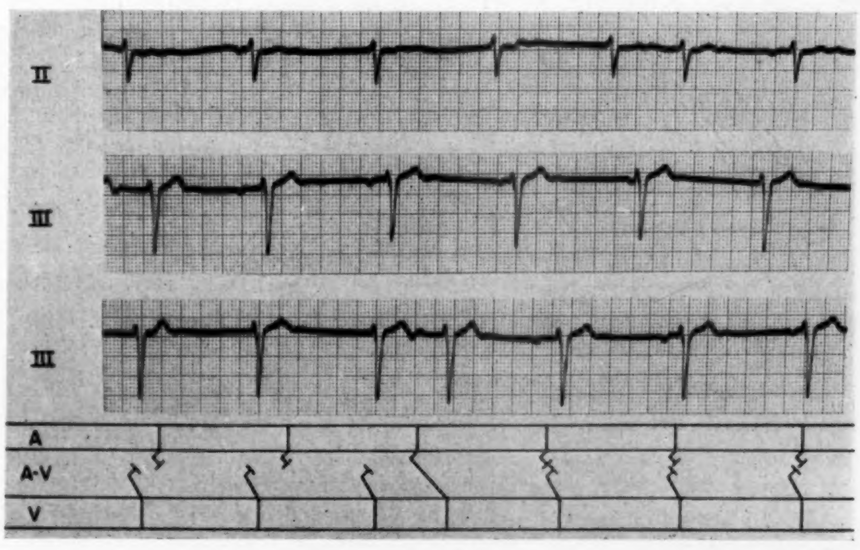

Fig. 4.—Dissociation with interference between pacemakers located, one at the uppermost region of the A-V conducting system, and the other, before the bifurcation of the common bundle. The middle and lower strips are continuous. (For discussion see text.)

the existence of an upper A-V rhythm was considered, its rate being 44 per minute. These deflections are slower than, and independent of (except on two occasions which shall be discussed below), the ventricular complexes. Also, they fall on different portions of the ventricular cycle; the duration of the latter being 1.24 to 1.26 second (corresponding to a rate of 47 to 48 per minute faster than the rate of the atria). Within a certain range, those P waves appearing around 0.36 second

after the preceding QRS complexes are conducted to the ventricles (sixth ventricular complex of the upper strip, and fourth complex of the lower strip). These interference beats have the same morphology as the spontaneous A-V ones; therefore, it is inferred that the pacemaker responsible for ventricular activation is located somewhere above the bifurcation of the common bundle. Thus, it can be clearly appreciated that in this case (as in Case 1) we are dealing with an A-V dissociation in which both pacemakers are located within the A-V conducting system.

Again, in the conducted beats some degree of A-V block exists, as can be deduced from the fact that the corresponding P-R intervals are prolonged (0.32 to 0.34 second). Two days after withdrawing digoxin the patient exhibited sinus rhythm with a somewhat prolonged A-V conduction time (0.26 second).

COMMENT

Inverted P waves in Leads II and III, which were present in Figs. 1, 2, and 4, favor the assumption of an A-V nodal rhythm,[10] its mechanism being obvious from the inspection of Table I. It can be appreciated from Table I that in almost all published examples of this arrhythmia the rate of the upper A-V center was under 87 per minute, so that a primary depression of the sinus node was considered probable. Yet, such a high frequency was seen in only one of our tracings, when the sinus pacemaker recorded 97 to 107 times per minute. These rates are, on the average, slightly slower than the ones observed when the electrocardiographic picture is solely that of nonparoxysmal upper A-V tachycardia, as was reported by Pick and Dominguez.[11] In their article the ectopic frequencies, expressed in beats per minute, were: 75 (Case 16), 85 (Case 20), 107-130 (Case 18), and 136 (Case 19).

TABLE I. RATE (BEATS/MIN.) OF ECTOPIC FOCI IN CASES OF DISSOCIATION WITH INTERFERENCE BETWEEN PACEMAKERS LOCATED WITHIN THE A-V CONDUCTING SYSTEM

	UPPER PACEMAKER	LOWER PACEMAKER
A. Observations From the Literature		
1. Luten and Jensen[1]	58–59	71–74
	62–65	71–76
2. Schott[2]	40–42	42–46
3. Barker[3]	68–71	73–75
B. Personal Observations		
Case 1 (Fig. 1)	79	100
Case 1 (Fig. 2)	86	91–97
Case 2 (Fig. 4)	44	47–48

Such a difference is understandable, because a faster upper automatic center should have a tendency to suppress a lower one, so that a simple tachycardia would result, without any dissociation. Similarly, a simple tachycardia would also be seen if the lower pacemaker had no retrograde block. The existence of the latter is a necessary postulate for the production and maintenance of dissociation with interference. However, some degree of forward block must be present,

because in Figs. 1 and 2 conducted beats failed to appear when expected, and, furthermore, after the presence of concealed A-V conduction, a prolonged P-R interval was observed whenever auriculoventricular conduction was reinitiated (Fig. 3).

Luten and Jensen[1] were the first to analyze an arrhythmia such as the one published here, and it is to be emphasized that their tracings also showed instances in which concealed conduction occurred, although this phenomenon was interpreted differently by them.

In a record similar to that of Luten and Jensen, Schott[2] demonstrated the transitory nature of this form of dissociation with interference, as well as the difficulties in establishing the correct diagnosis. He clearly outlined how reciprocal beats in A-V rhythm with posterior stimulation of the atria and gradually lengthening R-P intervals were able to produce misleading electrocardiograms. This is so because after the re-entry beats certain changes in the sequences of auricular and ventricular deflections are produced which can be easily mistaken for dissociation with interference. As early as 1925, Scherf and Shookhoff,[12] when studying the effects of induced premature systoles on A-V rhythm, clearly described the transitory alteration in the timing of the auricular deflections in the complexes following the extrasystoles. This alteration depended upon the speed of conduction below the A-V nodal pacemaker. These investigators also presented evidence of how ventricular extrasystoles without retrograde conduction to the atria (as reciprocal beats may be so considered) were succeeded by simultaneous activation of atria and ventricle, or by preatrial activation, in the type of A-V rhythm under consideration.

Other authors of that time estimated that these variations were due to a shift of the pacemaker in the A-V node.[16] But a simpler explanation was the one which attributed the changes in the A-V intervals to a fatigue in conduction always below the pacemaker (due to the premature systole), so that when the next A-V beat was produced, it found the atrial portions more responsive than the ventricular ones. Consequently, preceding activation of the atria took place.

In clinical cases, the significance and physiologic action of reciprocal rhythm is identical to that of the extrasystoles in the experiments quoted above, as can be concluded from studying Fig. 12 from the report of Fletcher and Stevenson.[13] In view of the previous arguments, the case reported by Barker (Reference 3, Figs. 300 and 301) is a clear example of dissociation with interference between pacemakers located within the A-V conducting system, so that his hypothesis of a wandering pacemaker in the A-V node is unnecessary. The correct interpretation of Barker's case is credited to Miller and Sharrett,[14] who outlined all theoretical possibilities concerning the foci between which dissociation with interference could occur. From an inspection of Fig. 1, it can be concluded that no beats from the upper pacemaker were conducted to the ventricles. On the contrary, occasionally conducted impulses were seen in Figs. 3 and 4. Nevertheless, in Fig. 2, and in certain parts of Fig. 3, some of the upper nodal, or sinus beats, made an attempt to traverse the A-V conducting system. This attempt was incomplete, the stimulus being blocked at certain levels of the latter. Its effect was revealed only by the unexpected failure of the following beat from the same

pacemaker to appear when due. Furthermore, in Fig. 3 it was appreciated that such a concealed A-V conduction affected initially an ectopic focus located before, and, lastly, one located after, the bifurcation. The varying extent of penetration through the A-V junction could have been produced, as indicated by Langendorf and Pick,[9] by extraneous influences, such as variations in vagal tone, or alterations in the duration of the length of the preceding ventricular cycles, hence of the refractory periods. These two factors may be present with either normal or depressed conductivity. Since it was shown that A-V conduction was depressed during the inscription of this record, another factor could have been responsible for this varying penetration, namely, a supernormal phase of recovery. Consequently, it is conceivable how an impulse that otherwise would be blocked is able to penetrate into the conducting tissues whenever a supernormal phase is present.[9] Yet, in the tracing being discussed all three factors are probably operating.

The possibilities that various pacemakers could exist side by side in specific cardiac muscle were considered many years ago by the German authors.[5-7] They referred mainly to the Purkinje fibers, and their papers dealt chiefly with the nature of the "protection" of the automatic centers, a matter which is beyond the scope of this paper.

Evidently, the arrhythmia featured in our records represents an enhancement of spontaneous A-V activity. When classified according to the ectopic rate, these manifestations adopted a passive (Fig. 4) as well as an active form (Figs. 1-3). In consequence, when the frequency of both pacemakers is fast enough (over 70), as in the first and second electrocardiograms, it is possible to make the diagnosis of simultaneous, independent, nonparoxysmal A-V tachycardias, a variety of double tachycardia not previously described.[15]

Another point of interest which was present in our patients, and in Luten and Jensen's, is the production of these disorders of rhythm by digitalis intoxication. From the clinical standpoint this is the most important feature, together with its occurrence in old people with arteriosclerotic heart disease and congestive heart failure. Further digitalization is prone to continue this disorder if no electrocardiograms are taken, for the ectopic rhythm can be easily mistaken for sinus rhythm accompanied (or not) by intermittent extrasystoles. Considering the possible increase in the ventricular rate,[11] which can easily worsen the clinical status, we would emphasize a withdrawal of digitalis as soon as the correct interpretation is made. As a matter of fact, the enhancement of A-V centers by this drug is not an unexpected finding.[10] However, in Figs. 1 and 4 we had to postulate a marked depression of the sinus node, to such a degree as to allow the upper A-V center to command the atria, although it is not definitely known whether we were dealing with a true sinus depression or with some degree of sinoauricular block. The latter possibility is suggested strongly by the finding of other disturbances of impulse conduction throughout the tracings.

SUMMARY

Dissociation with interference occurred between pacemakers located, one at the uppermost region of the A-V junction, and the other, either above or

below the bifurcation of the common bundle. A prolonged A-V conduction time of interference beats permitted the assumption that some degree of A-V block accompanied this form of dissociation. When both foci discharged at a high enough rate (over 70), it was then possible to make the diagnosis of simultaneous, independent, coexisting A-V tachycardias, a form of double tachycardia not previously described.

In some records of Case 1, occasional stimuli which had their origin in the uppermost pacemaker were stopped at different levels of the auriculoventricular conduction system; the effect of this was revealed only by the unexpected failure of the succeeding beat from the same pacemaker to appear. The varying extent of penetration depended on diverse causes, which were discussed and analyzed. This physiologic phenomenon, known as concealed conduction, had been described by Langendorf, and is observed when dealing with normal as well as with depressed conductivity.

The most important consideration from the clinical standpoint was the production of the arrhythmia by digitalis toxicity in old persons with arteriosclerotic heart disease and congestive heart failure. Prompt withdrawal of the drug is emphasized.

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Iproniazid (Marsilid) in Angina Pectoris

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In 1957, first Cesarman,[1] of the National Heart Institute of Mexico City, and then Cossio,[2] of Buenos Aires, published accounts on the use of iproniazid (Marsilid) in the treatment of angina pectoris. Cesarman noted the remarkable effect of this drug "serendipitously," that is, by pure chance.[3] Some of his cardiac patients had been depressed and were being treated with iproniazid, a "psychic energizer." To Cesarman's surprise, the anginal syndrome disappeared in every single case. These two investigators then began to study the direct effect of iproniazid on angina pectoris.

In both studies, 50 mg. of iproniazid was given 3 times daily, after meals, for periods ranging from several days to several months. Every one of Cesarman's 72 patients was subjectively benefited.[1a] The number of anginal attacks was reduced, often within 3 or 4 days. Usually, by the eighth or tenth day the cardiac pain completely disappeared, even in those patients who had previously required many tablets of nitroglycerin daily. Effort capacity increased. Furthermore, when the drug was discontinued, symptoms reappeared after 4 to 12 days. If the dosage was reduced, angina recurred, but was less severe than it had been prior to therapy. Side effects were not considered serious enough to warrant termination of treatment.

The abnormal resting electrocardiogram often improved, and in 8 patients an abnormal Master "2-step" test became negative. Because of this, Cesarman suggested that iproniazid probably acts directly on the etiological factors producing angina pectoris.

Cossio's results, though less striking, were, nonetheless, remarkable. Among his 36 patients the anginal syndrome disappeared completely in 40 per cent, was reduced in intensity and frequency in 30 per cent, and was not measurably benefited in the remaining 30 per cent. The side effects noted seemed well tolerated, and could be controlled easily by reduction in dosage of the drug. However, unlike Cesarman,[1,1a] Cossio[2] failed to note any improvement either in the abnormal resting electrocardiogram or in the results of the Master "2-step" test. He postulated that iproniazid in no way affects the underlying coronary artery disease. Four patients of the 36 sustained a coronary occlusion; one of these died. A fifth patient developed "syncope" and died. Cossio concluded that iproniazid was the most useful and promising drug yet developed for the treatment of angina pectoris.

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Because millions of patients the world over are crippled or incapacitated by the ravages of angina, any drug that holds out hope for successful treatment of it should be eagerly welcomed and investigated. I, therefore, sought to confirm the promising observations on iproniazid. Furthermore, there were fundamental differences in the reports of these two authors. In one, all patients benefited, with associated electrocardiographic improvement.[1,1a] In the other, there was good subjective improvement, but this was unaccompanied by any significant objective evidence.[2]

This present study comprises 74 patients suffering with typical and severe angina pectoris. There were 58 men and 16 women, chiefly between the ages of 50 and 70 years (Tables I and II). Among these patients, 6 were in "status anginosus" and required from 20 to 60 tablets of nitroglycerin daily (Table II). Most of the others had from 2 to 20 attacks daily; 6 patients who were able to avoid the precipitating factors, experienced only a few episodes each week.

Each patient was given 50 mg. of iproniazid 3 times daily after meals. In addition, in the hope of preventing the development of a peripheral neuritis and dryness of the mouth, 25 mg. of pyridoxine was prescribed routinely with each dose of iproniazid. Vasodilators, with the exception of nitroglycerin, when necessary, were not employed. If heart failure was present, it was treated by the usual means.

TABLE I. AGE AND SEX DISTRIBUTION OF 74 PATIENTS

	Average Age: Male	59 years	
	Female	63 years	
		Males	*Females*
40–49 years		8	1
50–59 years		26	2
60–69 years		18	9
70–79 years		6	4
		58	16

The course of treatment with iproniazid lasted for from 1 week to 5 months. Of the 74 patients given a therapeutic trial, 17 still use the drug (2 had stopped but then resumed). Severe side reactions compelled the discontinuance of iproniazid in the remainder. Further undesirable side effects, together with reports of hepatocellular necrosis, have since prompted complete cessation of iproniazid therapy in all patients. In some patients the drug was tolerated for only 1 month or less.

RESULTS

Thirteen patients of the 74 lost their angina completely and were able to perform normal tasks with confidence and without any pain whatsoever. In another 28, cardiac pain was almost completely relieved, but could be reproduced occasionally with severe exertion (Tables II and III). Hence, in more than half

TABLE II. IPRONIAZID IN ANGINA PECTORIS (74 PATIENTS)

NO.	NAME	AGE (YR.)	SEX	DURATION OF TREATMENT	FREQUENCY OF PAIN AND PRESSURE		OUTCOME; REASON IF DISCONTINUED
					BEFORE	AFTER	
1.	I.A.	45	F	5 mo. +	4 times a day	twice a wk.	Improved, still on therapy
2.	W.H.B.	64	M	4 mo. +	3-4 times a day	none	Improved, still on therapy
3.	D.B.	52	M	4½ mo. +	20 times a day	5-6 times a wk.	Improved, still on therapy
4.	G.C.	58	M	3 mo. +	2-3 times a day	once a day or less	Improved, still on therapy
5.	E.D.	72	F	3½ mo. +	5 times a day	none	Improved, but stopped, then resumed treatment
6.	H.E.	59	M	4 mo. +	1-2 times a day	1-2 times a wk.	Improved, still on therapy
7.	R.F.	61	M	4½ mo. +	4-5 times a day	3 times a week	Improved, still on therapy
8.	H.G.	47	M	1 mo.	1-2 times a day	none	Improved, but sustained coronary insufficiency
9.	J.G.	52	M	3½ mo. +	twice a day	rarely	Improved, still on therapy
10.	J.G.	49	M	4 mo. +	3 times a day	5 times a wk.	Improved, still on therapy
11.	S.I.	48	M	5 mo. +	20+ times a day	none	Improved, still on therapy
12.	S.K.	66	M	3 mo. +	2-3 times a day	none	Improved, but died suddenly
13.	G.K.	63	M	3 mo.	50 times a day	none	Improved, but possible heart failure
14.	H.K.	67	M	5 mo. +	3-10 times a day	rarely	Improved, still on therapy
15.	L.L.	47	M	2 mo. +	twice a day	rarely	Improved, but became tremulous and gassy, resumed again
16.	N.M.	57	M	4 mo. +	3-4 times a day	4 times a wk.	Improved, still on therapy
17.	J.M.	59	M	4 mo. +	once a day	none	Improved, still on therapy
18.	S.S.	63	M	1 wk.	twice a day	rarely	Improved, but sustained coronary occlusion
19.	R.S.	64	F	3½ mo. +	10 times a wk.	2 times a wk.	Improved, still on therapy
20.	A.S.	60	M	4 mo. +	6 times a wk.	rarely	Improved, still on therapy
21.	H.Z.	51	M	6 wk.	3 times a day	none	Improved, but developed coronary occlusion and died
22.	R.A.	45	M	7 wk.	3 times a day	6 times a mo.	Improved, but impotent
23.	J.B.	54	M	2 wk.	20+ times a day	3-4 times a day	Improved, but severe back pain
24.	I.B.	59	M	1 mo.	3-4 times a day	none	Improved, but dizzy and impotent
25.	M.B.B.	59	M	2 mo.	few times a wk.	once a mo.	Improved, but dizzy
26.	F.B.	64	F	3 mo.	3 times a day	rarely	Improved, but alcohol not tolerated
27.	M.F.	72	F	6 wk.	5-6 times a day	2-3 times a day	Improved, but drowsy, edema in legs; coronary insufficiency 2 wk. after cessation
28.	M.R.	49	M	2 wk.	twice a day	once a day	Improved
29.	N.H.	62	M	1 mo.	4 times a day	once a day	Improved, but dizzy and pains all over
30.	S.H.	62	F	5 wk.	3-4 times a day	once a day	Improved, but severe headaches
31.	H.J.	55	F	1 mo.	1-2 times a day	twice a wk.	Improved, but drop in B.P.
32.	E.J.	73	M	6 wk.	1-2 times a day	few times a wk.	Improved, but neuritic pain
33.	J.K.	62	M	7 wk.	2-3 times a day	4 times a wk.	Improved, but developed mouth sores
34.	C.L.	73	M	7 wk.	2-3 times a day	none	Improved, but drop in B.P.
35.	H.M.	72	M	1 mo.	4 times a wk.	none	Improved, but became disoriented and had syncope
36.	J.S.	60	M	2 wk.	6 times a day	none	Improved, but urinary disturbance
37.	B.S.	60	F	9 wk.	10 times a day	once a day	Improved, but dizzy
38.	A.S.	42	M	10 wk.	few times a day	none	Improved, but developed hepatitis
39.	C.W.	69	F	5 wk.	1-2 times a day	rarely	Improved, but severe pain in back and legs; fainted
40.	S.Z.	59	M	1 mo.	1-2 times a day	3 times a wk.	Improved, but dizzy and gassy
41.	M.N.	60	M	2 mo.	20-25 times a day	twice a day	Improved, but developed prostatitis

TABLE II. IPRONIAZID IN ANGINA PECTORIS (74 PATIENTS)—(CONT'D)

NO.	NAME	AGE (YR.)	SEX	DURATION OF TREATMENT	FREQUENCY OF PAIN AND PRESSURE		OUTCOME; REASON IF DISCONTINUED
					BEFORE	AFTER	
42.	M.G.	60	F	1 wk.	once a wk.	?	Improvement doubtful
43.	H.H.	65	M	3 mo.	few times a mo.	few times a mo.	Improvement doubtful, urinary disturbance
44.	M.S.	60	F	1 mo.	50-100 times a day	?	Improvement doubtful, extreme dizziness
45.	B.Z.	58	M	5 wk.	15-20+ times a day	1-2 times a day, then 20-30 times a day	Improved, but aggravated later
46.	E.A.	58	M	5 wk.	3 times a wk.	3 times a wk.	No improvement
47.	E.B.	58	M	1 wk.	2-5 times a wk.	?	No improvement, extreme dizziness
48.	S.C.	57	M	1 mo.	few times a wk.	few times a wk.	No improvement
49.	H.C.	53	M	1 mo.	5 times a day	5 times a day	No improvement, patient was in heart failure
50.	J.D.	57	M	6 wk.	few times a wk.	few times a wk.	No improvement
51.	S.D.	55	M	6 wk.	5-10 times a wk.	5-10 times a wk.	No improvement
52.	L.J.D.	69	M	7 wk.	rarely	rarely	No improvement
53.	L.D.	75	M	1 wk.	twice a wk.	?	No improvement, dizzy and nauseated
54.	I.E.	53	M	1 mo.	few times a day	?	No improvement, drop in B.P., dizzy, then coronary insufficiency
55.	W.F.	61	M	7 wk.	1-2 times a day	1-2 times a day	No improvement, dizzy
56.	B.M.F.	61	M	1 mo.	twice a day	twice a day	No improvement, unpleasant taste in mouth
57.	L.G.	52	M	3 mo.	few times a wk.	twice a wk.	No improvement
58.	B.H.	54	F	2 wk.	10 times a day	10-15 times a day	No improvement, pain aggravated
59.	C.J.	66	M	1 mo.	3-5 times a day	1-4 times a day	No improvement, constipated
60.	M.K.	51	M	3 wk.	7-8 times a day	7-8 times a day	No improvement, urinary disturbance
61.	E.L.	62	F	2 wk.	few times a wk.	few times a wk.	No improvement, nauseated
62.	J.L.	48	M	6 wk.	once a day	once a day	No improvement, dizzy
63.	W.M.	58	M	2 wk.	few times a wk.	few times a wk.	No improvement, nauseated and drowsy
64.	M.M.	64	M	5 wk.	20+ times a day	worse	No improvement, pain aggravated
65.	M.N.	70	M	6 wk.	3 times a day	3 times a day	No improvement
66.	F.P.	72	F	1 wk.	3-4 times a day	3-4 times a day	No improvement, extreme dizziness
67.	J.P.	50	M	6 wk.	3 times a day	5 times a day	No improvement, pain aggravated
68.	M.G.	79	M	1 wk.	5 times a wk.	?	No improvement, dizzy and prostatitis
69.	A.S.	62	F	1 mo.	3-4 times a wk.	3-4 times a wk.	No improvement
70.	G.S.	68	M	2 wk.	4 times a wk.	4 times a wk.	No improvement
71.	I.S.	52	M	1 mo.	1-2 times a day	1-2 times a day	No improvement, dizzy, urinary disturbance, rapid heart
72.	J.T.	53	M	1 wk.	3-4 times a wk.	?	No improvement, severe headaches
73.	S.U.	79	F	2 mo.	1-2 times a wk.	1-2 times a wk.	No improvement
74.	J.W.	51	M	2 wk.	twice a day	twice a day	No improvement, gall bladder attack

of our patients, 41 in a total of 74, iproniazid relieved the anginal syndrome completely or almost completely. In 3 cases improvement was doubtful. In 29 patients the chest pain was not relieved. In one case improvement seemed to occur, but was later followed by an aggravation of pain.

When iproniazid was effective, symptoms were relieved within 3 to 10 days. The improvement persisted for as long as the drug was continued. When it was stopped, its antianginal effect usually lasted for periods ranging from a few days to 2 weeks, then slowly disappeared. In rare instances the beneficial effects were maintained for weeks, and in one case, for 2 months.

TABLE III. RELIEF OF PAIN IN 74 PATIENTS

Complete	13
Almost complete	28
Doubtful	3
Relief, then aggravation	1
No relief	29
Total	74

Electrocardiograms before and after treatment were available in 28 patients. In this group, 22 had experienced dramatic relief of angina, 5 were unchanged, and 1 showed an initial response and then deteriorated clinically. Of these 28 patients, only 2 showed any improvement in the abnormal resting electrocardiogram. In another 4 patients with an abnormal resting electrocardiogram prior to treatment there was slight or equivocal electrocardiographic improvement. In these 6 patients the changes are difficult to interpret because they had been developing even prior to iproniazid therapy. In 20 of these 28 cases, the abnormal resting electrocardiogram remained completely unchanged after treatment (Table V; Fig. 1). In 2 patients there was definite deterioration of the resting electrocardiogram, and in one of these an acute coronary occlusion occurred.

In 6 patients whose resting electrocardiogram was normal the Master "2-step" test[4] was positive. In none was there a change in the record after treatment with iproniazid (Table V; Fig. 2), although there was clinical improvement.

The side reactions are listed in Tables II and IV. The gastrointestinal effects were constipation, which in 25 patients was both annoying and severe. This was overcome, albeit with difficulty, by cathartics and Prostigmin. "Indigestion," flatulence, distention, abdominal discomfort, belching, and passing of wind occurred in 8 of the subjects. Intractable dryness of the mouth was present in 21 cases.

Genitourinary disturbances were common. Difficulty in micturition, polyuria, dysuria, and nocturia developed in 19 subjects, and impotence in 7. Of the latter 7, only 2 elected to continue the drug, 2 preferred anginal attacks to impotence and therefore discontinued treatment, while the other 3 refused the drug because of other side effects. In those who stopped the drug the impotence disappeared in a day or two.

Dizziness, which included lightheadedness and a slight feeling of faintness, occurred in 25 patients and was, perhaps, the most important and most common side reaction. For want of a better classification, we grouped dizziness together with a distinct drop in blood pressure (in 4 patients) and syncope (in another 3). Unfortunately, we were not present during any of the syncopal attacks and, therefore were unable to record blood pressure readings. In the 4 whose blood pressure fell without producing syncope, readings of 80 to 94 mm. Hg systolic and 50 to 60 mm. Hg diastolic were recorded.

Nine patients were definitely "energized" or "pepped up." Headache appeared 6 times and insomnia 5. On the other hand, 6 patients were profoundly fatigued, 3 of whom became very sleepy. It is not unusual to observe a patient suffering from heart disease who is easily fatigued, but in these 6 instances the fatigue and sleepiness were new and real.

Severe peripheral neuritis[5] developed in 4 patients. One of our cases (No. 11 in Table II; Case Report 3) had suffered from a neuritis in the right lower extremity for 3 years following a hemiplegia. This pain was much aggravated by iproniazid, but his angina pectoris disappeared and he has remained on the drug for 5 months.

TABLE IV. SIDE EFFECTS IN 74 PATIENTS

Gastrointestinal	
Constipation	25
Flatulence	8
Dryness of Mouth	21
Hepatitis	1
Genitourinary	
Urinary Disturbances	19
Impotence	7
Cardiovascular (?)	
Dizziness	25
Blood Pressure Drop	4
Syncope	3
Cerebral (?)	
Cerebral Stimulation	9
Headaches	6
Insomnia	5
Fatigue and Drowsiness	6
Neurological	
Neuritis	4
Miscellaneous	
Weight Gain	4
Diaphoresis	3
No Side Effects	14

Four patients gained weight, perhaps because of an increase in appetite or a retention of sodium. There was no clinical evidence of edema. One patient, who previously had been distinctly overweight, gained an additional 20 pounds in 4 months of treatment. He described his appetite as "ravenous."

Profuse sweating occurred in 3 patients but was not sufficient cause for cessation of treatment. Severe muscle twitching (fasciculation) and "shakes" did occasionally develop. A few patients apparently developed nightmares after taking iproniazid, but this finding was not important. Rarely, alcohol was not tolerated; in one case the patient (No. 26 in Table II) elected to stop the iproniazid because he preferred his occasional drink. One case of transient hepatitis occurred (No. 38 in Table II).

TABLE V. ELECTROCARDIOGRAM AND MASTER "2-STEP" TEST

Effect on Control Electrocardiogram		28
No Improvement	20	
Improvement	6	
4 slightly improved but had been improving prior to treatment		
2 definitely improved but had been improving rapidly prior to treatment		
Aggravation	2	
1 coronary occlusion		
1 definitely worse		
Effect on Master "2-Step" Test		6
6 unchanged		

CASE REPORTS

Relief of Status Anginosus.—

CASE 1.—G. K. (No. 13, Table II), a 63-year-old man, has had an anginal syndrome for many years. His heart was enlarged; he has been in heart failure. At the age of 55 he sustained a coronary occlusion. For the past 3 years he has been in "status anginosus." A severe anxiety state and emotional instability were aggravating factors. The frequency of his attacks necessitated the taking of nitroglycerin 50 times daily. With the use of iproniazid, the symptoms disappeared almost magically. Nitroglycerin was no longer required. However, the objective evidence of his heart failure did not lessen nor was his abnormal electrocardiogram altered.

Relief of Angina Pectoris.—

CASE 2.—H. K. (No. 14, Table II), a 67-year-old man, was first seen about 4 years ago with a typical anginal syndrome. The patient was extremely intelligent, but very worried and apprehensive because of his disease. He was, indeed, in an anxiety state. Attacks occurred 10 times a day, although he zealously avoided undue physical exertion and took nitroglycerin to prevent them. Without these precautions, his attacks would undoubtedly have been much more frequent. A few days after treatment with iproniazid was begun, clinical improvement was evident and continued for 5 months. The development of polyuria and nocturia necessitated a decrease in the dosage of iproniazid to 100 mg. daily. The symptoms, however, did not reappear with this reduced dosage. The patient's resting electrocardiogram had always been essentially normal, but the Master single "2-step" test before treatment was distinctly positive. After 5 months of iproniazid therapy there was no qualitative or quantitative change in the RS-T segment after standard exercise (Fig. 2).

Relief of Status Anginosus but Aggravation of a Peripheral Neuritis.—

CASE 3.—S. I. (No. 11, Table II), a 48-year-old man, had an anginal syndrome for 9 years. He had had 2 attacks of acute coronary insufficiency with subendocardial infarction, and one

coronary occlusion. In 1949, an upper dorsal bilateral sympathectomy for relief of the thoracic pain was unsuccessful. There was marked emotional instability. For years, he has been in "status anginosus," for which he took 20 to 60 tablets of nitroglycerin a day; he literally lived on this drug. No other medication had ever been efficacious, and scores of them had been essayed. A few days

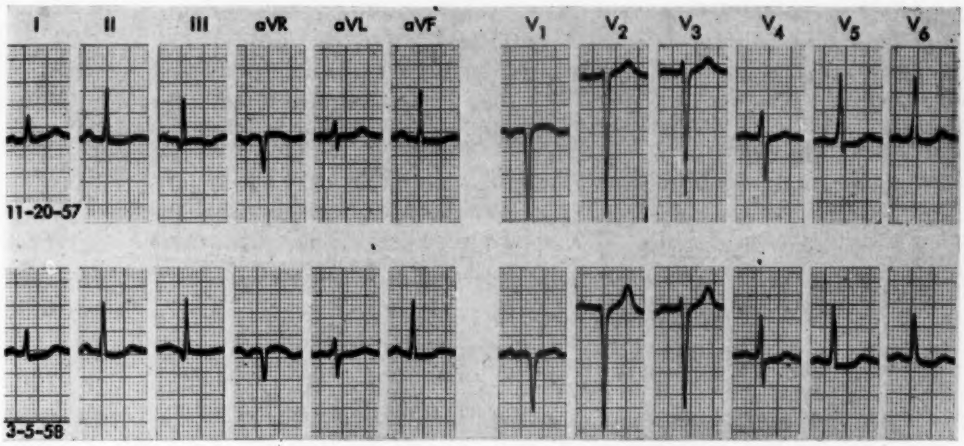

Fig. 1.—S. I., male, 48. Status anginosus: previous coronary occlusion (once) and previous coronary insufficiency (twice). Q in Lead V_1; rS pattern in Leads $V_{1,2}$, with RS-T segment depressions in Leads II, III, aV_F, and $V_{5,6}$. Not altered after 5 months of Marsilid.

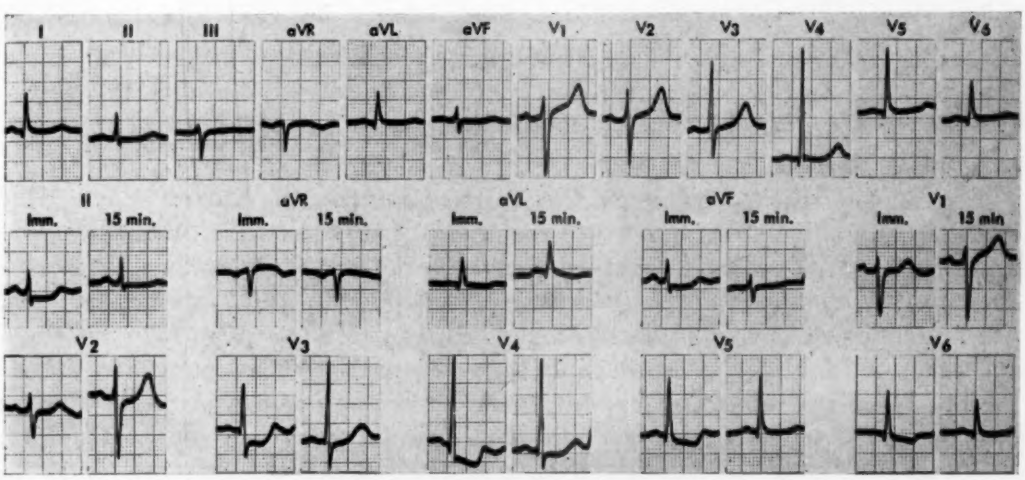

Fig. 2.—H. K., male, 67. Angina pectoris for many years. The resting electrocardiogram had been normal, but the Master "2-step" test was always abnormal. The test was as significantly positive after 3 months of Marsilid therapy as before. Actually, the RS-T segment depressions and the T-wave inversions after exercise did not return to normal at the end of 15 minutes, although they were not so pronounced as immediately following the test. Usually, the changes disappear within 6 minutes.

after treatment with iproniazid was instituted the symptoms disappeared. For 5 months, until the time of this report, he experienced no angina, even though he engaged in strenuous exertion. The control electrocardiogram, however, did not show any improvement (Fig. 1). Three years ago, following a hemiplegia, the result of an embolus from a mural thrombus of the left ventricle,

severe pain in the right lower extremity had developed. This has become aggravated despite the addition of pyridoxine to the iproniazid. The patient gained 20 pounds in weight during the 4 months of iproniazid therapy; his appetite became "ravenous." There was, however, no evidence of heart failure.

Relief of Angina but Development of Coronary Insufficiency.—

CASE 4.—H. G. (No. 8, Table II), a 47-year-old man, had a long history of coronary disease with an anginal syndrome. He had suffered a coronary occlusion, but had done well following it. Because his chest pain reappeared, treatment with iproniazid was instituted in November, 1957. The chest discomfort disappeared thereafter, but, nevertheless, an episode of acute coronary insufficiency developed 3 weeks after the iproniazid treatment was started. Although the attack of coronary insufficiency may be a coincidence, it is clear that iproniazid did not modify the progression of the underlying coronary sclerosis.

No Relief; Development of Coronary Occlusion With Death.—

CASE 5.—H. Z. (No. 21, Table II), a 51-year-old man, gave a classical history of anginal syndrome for 2½ years. In June, 1957, he developed an episode of acute coronary insufficiency. Treatment with iproniazid was begun on Dec. 28, 1957, but he developed a coronary occlusion on Jan. 15, 1958, and died.

DISCUSSION

The effect of iproniazid on the anginal syndrome is indeed remarkable. Forty-one in a series of 74 seriously sick patients obtained complete, or near complete, relief of chest pain. Of the 6 patients in "status anginosus" 5 became entirely free of pain! I have never seen anything like it in my many years of practice and interest in coronary disease. I thus agree with both Cesarman[1] and Cossio[2] that iproniazid is effective in alleviating the subjective symptoms of angina pectoris. However, any enthusiasm is very much tempered by the observation of serious and toxic side effects produced in patients receiving the drug. Because of the side effects one is compelled, regretfully, to limit its use at the present time to those patients in whom desperate measures are justified. Even then, one should hesitate to use the drug at all in private practice.

At present, the mechanism of the action of iproniazid is obscure and entirely speculative. It is known to be, as are many other agents, an inhibitor of monoamine oxidase, an enzyme involved in the breakdown of serotonin (5 hydroxytryptamine), epinephrine, norepinephrine, and possibly other amines.[6] Thus, the stimulant effect of iproniazid on the central nervous system may well be a reflection of its ability to protect or spare serotonin and norepinephrine in the brain. Iproniazid apparently prevents the serotonin in the brain, and possibly that in the heart, from being destroyed by the enzyme monoamine oxidase.

The precise means by which iproniazid produces symptomatic relief in angina pectoris is unknown. While serotonin does have certain cardiovascular effects, it is doubtful whether it relieves the pain in angina pectoris.[6-8] Reserpine, which is so commonly employed in clinical medicine, and which likewise increases the supply of serotonin in the body, does not relieve angina pectoris. Conceivably, the relief of chest pain may occur because of an effect on the autonomic nerve connections between the heart, on one hand, and the brain and spinal cord, on the other.

Pletscher and Pellmont[9] have demonstrated a striking rise in the catecholamine content of the heart of guinea pigs treated with iproniazid. This could be

related to the therapeutic response, although it would be counter to the theory of Raab,[10] who has maintained for years that the catecholamines, e.g., epinephrine, norepinephrine, are the factors that produce, rather than relieve, pain in coronary disease.

Cesarman[1] postulates some influence on cardiac metabolism, perhaps some enzymatic response, to explain the phenomenon of pain relief. Cossio[2] believes that the antianginal effect is due to a selective block of the "P" substance of Lewis, the pain-producing agent which is produced under ischemic conditions.

In my opinion, the relief of angina pectoris by iproniazid is due, at least in part, to cerebral stimulation, with uplift of mood and increase of the pain threshold. In the field of psychiatry, iproniazid has been employed with success as a "psychic energizer."[11] In our study of 74 patients the greatest benefit seemed to occur in the most apprehensive patients.

Patients receiving iproniazid often exhibit serious and debilitating side effects, probably originating chiefly from the nervous system. Although there is no proof that iproniazid is a ganglionic blocking agent, one is reminded that many of its side effects are similar to those of the antihypertensive ganglionic blocking drugs. On the other hand, ganglionic blocking drugs do not relieve anginal pain. In any event, it seems justifiable to attribute the gastrointestinal and the genitourinary manifestations to alterations in autonomic nerve balance. Included in the effects on the central and peripheral nervous systems are mental exhilaration, insomnia, reduced requirements for sleep,[11] peripheral neuritis, hyperreflexia, muscular twitching, and tremors.[12-14] It has already been mentioned that 25 mg. of pyridoxine, when dispensed with each dose of iproniazid, seemed to minimize the peripheral neuritis, dryness in mouth, and disturbances in urination. Whether it actually prevents side effects is doubtful.

Dizziness, which we grouped with fall in blood pressure and syncope, may be the result of direct brain stimulation or interference with labyrinthian function. A pronounced orthostatic effect has been observed in hypertensive patients.[15] Cossio[2] observed a drop in blood pressure in 40 per cent of his patients. In his published table the fall is only slight or occasionally moderate. Nevertheless, it is logical to assume that the decrease in blood pressure was the cause of syncope with death in one of his patients, and may very well have been a factor in another sudden death due to coronary occlusion, as well as in the precipitation of coronary occlusion in 3 other instances.* We have shown that a fall in blood pressure in shock may precipitate coronary occlusion[16] because of the alteration in the coronary circulation with resultant thrombosis. This mechanism may have been responsible also for our 2 instances of coronary occlusion, resulting in the death of one patient, and for our 3 episodes of coronary insufficiency[17] with subendocardial ischemia and necrosis. Possibly, iproniazid, through its effect on the blood pressure center in the medulla, may cause the drop in blood pressure. However, 3 cases of coronary insufficiency and 2 of coronary occlusion among 74 patients may be a pure coincidence, since, for the most part, they were gravely sick people. One, therefore, cannot be certain at present whether or not iproniazid

*I have been informed of a fall in blood pressure to 60 mm. Hg systolic.

is a cause of coronary accidents, but it is suspect, and it does indicate the great care with which the patients must be watched.

In a patient with coronary disease, induced or spontaneous coronary insufficiency is an ever present danger.[17] Since postural hypotension is not uncommon during treatment with iproniazid, the blood pressure should be taken frequently, perhaps daily, especially in those who have normal blood pressure. It should be recorded in the standing position, as well as in the sitting or recumbent positions. This may not be as essential in those with hypertension. In patients who regularly possess a low blood pressure, e.g., under 100 mm. Hg systolic, the drug is probably contraindicated. One occasionally finds this low blood pressure in patients who have recovered from a coronary occlusion.

A distinct fall in blood pressure, e.g., to below 100 mm. Hg, is an indication for discontinuance of treatment with iproniazid. The drug may be resumed when the blood pressure has returned to safe levels, but smaller doses should be employed. Normal arterial pressure levels may not be obtained for from 2 to 3 weeks, since iproniazid is retained by the body for some time. In addition to possible cardiovascular complications, the physical danger of actual syncope is obvious; thus, a fall and resultant broken tibia has been described.[12]

Because of the hypotensive effect, the patient using iproniazid should be advised to sit or lie down before taking his nitroglycerin. Although I have no proof in any single instance, it is self-evident that if this drug is taken by a patient who already has a low blood pressure, the postural hypotension, plus the further lowering of the blood pressure by this vasodilator, may result in serious complications.

The euphoria engendered by iproniazid, although it may possibly explain the relief of angina, is at the same time a possible cause of induced coronary insufficiency.[17] The mental exhilaration, with the disappearance of fatigue and the appearance of restlessness, the muscle twitchings, and tremors, the increased physical activity, may increase the work of the heart out of proportion to its blood supply. This is doubly dangerous if the threshold of pain is raised, whether it be in the brain or heart, or both.

A gain in weight may be due to a "ravenous" appetite (Case Report 2; No. 11 in Table II) or may be an indication of heart failure with salt and water retention. Peripheral edema has been reported.[5] As we have indicated, our patients with heart failure were treated with the usual means, including digitalis, diet, and diuretics. Therefore, this basic therapy may have minimized any accumulation of salt by iproniazid if there were such a tendency. Further studies will undoubtedly clarify this matter.

Hepatitis (Tables II and IV), presumably related to iproniazid therapy,[12] occurred only once in our series.

The remarkable subjective improvement in angina with the use of iproniazid has been emphasized repeatedly. However, there was no evidence of an effect on the coronary disease, per se, in my cases. The objective study of the resting electrocardiogram and the Master "2-step" test[4] is of great importance in analyzing the mode of action of iproniazid. The ordinary resting electrocardiograms when repeated in 28 patients who had been on iproniazid for months did not

indicate in any one of them an unequivocal improvement (Table V; Fig. 1). It is true that in 6 of the 28 some electrocardiographic improvement appeared, but this had already been developing before the patients were placed on the drug.

Similarly, although the 6 patients with normal resting electrocardiograms who performed the Master "2-step" test[4] had been completely relieved of their anginal symptoms, not a single one demonstrated electrocardiographic improvement after the standard exercise (Table V; Fig. 2).

Because neither the resting nor the Master "2-step" electrocardiogram is altered after iproniazid therapy, we agree with Cossio[2] that the preparation probably has no effect on the fundamental causes of coronary artery disease. As further proof of this belief, we repeat that 3 of our patients sustained an attack of acute coronary insufficiency during treatment, and 2 others, one of whom died, developed acute coronary occlusion. Cossio's results were even more pronounced, for in his 36 patients, he perceived 4 who sustained a coronary occlusion, with one death, while a fifth person developed syncope and died.

With the dangerous side effects following iproniazid therapy which we have discussed, what is the future of this drug? The manufacturer must search for an analogue or a drug to be combined with iproniazid which will not only relieve pain but will have no dangerous side effects. Perhaps a vasopressor drug such as ephedrine, or similar preparation, may be prescribed with iproniazid to maintain a normal blood pressure level. Finally, a preparation which would improve the coronary circulation, increase the efficiency of oxygen utilization or extraction by the myocardium, or heal the arteriosclerosis, should be the goal we strive to attain. I believe that there is enough promise in iproniazid to justify its continued investigation under research conditions.

SUMMARY AND CONCLUSION

Seventy-four patients with severe angina pectoris were treated with iproniazid, beginning with 150 mg. daily, for from 1 week to 5 months.

In my long experience with innumerable drugs for coronary disease, not one has approached the subjective relief attained by iproniazid.

In more than one half of the patients, 41 to be exact, iproniazid relieved the anginal syndrome completely or almost completely. Five of these patients were in "status anginosus." In 29 patients there was no relief of pain; one of these was a case of "status anginosus."

Neither the resting electrocardiogram nor the Master "2-step" test was altered during the course of treatment with iproniazid, indicating that the fundamental coronary disease was not altered, at least in this 5-month period.

The precise mechanism of the relief of pain by iproniazid is unknown. It can possibly be explained by cerebral stimulation, with uplift of mood, and increase of the pain threshold. There may be a direct effect on the autonomic nerve connections between the heart and the spinal cord and brain.

The side effects were mainly gastrointestinal, genitourinary, and cardiovascular, the latter including dizziness, fall in arterial pressure, and syncope. Less common complications were evidences of cerebral stimulation, peripheral neuritis, dryness of the mouth, hepatitis, and gain in weight. One case of hepa-

titis occurred, with subsequent recovery. Four patients noted significant gain in weight.

The fall in blood pressure is probably a factor in syncope and in episodes of acute coronary insufficiency. It may possibly be a factor in the precipitation of coronary occlusion.

The physical overactivity associated with euphoria, excitement, and loss of pain, may cause coronary insufficiency.

The patient receiving iproniazid should be supervised very closely. Blood pressure should be measured in the standing position. On the other hand, nitroglycerin should never be taken by the patient except in the sitting or recumbent position.

In view of the numerous side effects, some of which are dangerous, iproniazid should be studied further only in hospitals and by research teams. It is to be hoped that diligent investigators will continue to seek an analogue of iproniazid which will relieve angina, and will not be dangerous.

I wish to thank my associate, Dr. Ephraim Donoso, and my technician, Mrs. Gertrude Reis, for their indefatiguable cooperation.

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Corrected Transposition of the Great Vessels of the Heart

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Recently, at the Indiana University Medical Center, we have had an opportunity to study, both clinically and pathologically, 3 cases of a congenital cardiovascular anomaly heretofore seldom diagnosed. This condition is termed "corrected transposition of the great vessels of the heart." In one of these cases the diagnosis was made clinically, and was subsequently confirmed at autopsy. The other two cases were diagnosed at autopsy.

This condition is easily misdiagnosed, both clinically and pathologically. Recent evidence indicates that it is not nearly so rare as might be indicated in the literature. A complete review of the world's literature prior to 1957, reveals only 42 cases of corrected transposition, most of which were not diagnosed clinically, but only at autopsy. However, in 1957, Anderson and associates,[1] of the University of Minnesota, reviewed 17 additional cases, all diagnosed clinically within a period of less than 5 years. We are reporting the 3 cases of corrected transposition of the great vessels of the heart which have come to autopsy at Indiana University Medical Center within the past 2 years.

ANATOMY

Before one can understand the anatomic features of corrected transposition of the great vessels, it is essential to have in mind the anatomic features of the more common "uncorrected" transposition of the great vessels (usually referred to simply as transposition of the great vessels).

In the normal heart the ascending aorta arises posterior to and slightly to the right of the pulmonary artery. As they course superiorly, the aorta and pulmonary artery cross. Normally, the aorta carries oxygenated blood from the left ventricle, and the pulmonary artery carries venous blood from the right ventricle.

In transposition of the great vessels (at least in its complete form; various incomplete varieties of transposition will not be discussed here) the aorta arises exclusively from the right ventricle, and the pulmonary artery arises from the left ventricle. The aorta arises anterior to, and in a plane very slightly to the right of, the pulmonary artery. The two vessels run parallel to each other and do not cross in the usual manner. Thus, in transposition, the anteroposterior relation of the aorta and pulmonary artery is reversed. If no other cardiac

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anomalies are present, this condition is incompatible with life; there are two mutually independent circulations, one carrying unoxygenated blood through the right ventricle and out into the aorta and systemic circulation, the other carrying oxygenated blood from the lungs, through the left side of the heart, and out to the lungs again. Frequently, an additional anomaly permits mixing of the greater and lesser circulations; the most frequent of these anomalies are patent foramen ovale, interventricular septal defect, and patent ductus arteriosus. Although patients with these anomalies are usually severely cyanotic, their chance for survival is greatly enhanced by the amount of mixing of the circulations permitted by these three types of communication.

In corrected transposition of the great vessels the ascending aorta and pulmonary artery are related to each other in the anteroposterior plane as in transposition of these vessels; the aorta lies anterior to the pulmonary artery, and the two vessels run parallel to each other without crossing. However, the aorta arises from the ventricle on the left side and the pulmonary artery from the ventricle on the right, and the aorta arises to the left of the pulmonary artery. Thus, since the venous connections of the heart are normal, the aorta carries oxygenated blood and the pulmonary artery venous blood, and this peculiar arrangement, per se, produces no physiologic disturbance and is of no functional consequence.

However, most cases of corrected transposition of the great vessels are associated with other cardiac anomalies. In most cases, including the 3 in our series, there is an associated localized situs inversus of the ventricles. It should be noted that "inversion" implies reversal of position in a right and left plane. The left-sided ventricle, which delivers oxygenated blood to the aorta, possesses the morphologic features of a normal right ventricle, with coarse trabeculae carneae, a tricuspid atrioventricular valve, and a crista supraventricularis delimiting a conus arteriosus. The right-sided ventricle, which delivers venous blood to the pulmonary artery, has the morphologic features of a normal left ventricle, with delicate trabeculae carneae, a bicuspid atrioventricular valve, no crista supraventricularis, and no pulmonary conus. Frequently, there is also situs inversus of the coronary arteries, although both arise from the aortic valve; it is the right-sided coronary artery that divides into anterior descending and circumflex branches.

The anomalies described above are of great interest morphologically, but of little significance functionally or clinically. Other associated abnormalities are often of great significance, and are of widely assorted types. Among the 17 patients studied by Anderson, the most frequently associated anomalies were interventricular septal defect and pulmonary stenosis. Anderson's series included 6 cases with associated ventricular septal defect, 1 with a ventricular and an atrial septal defect, 1 with a ventricular septal defect and left atrioventricular stenosis, 3 with pulmonary stenosis, 1 with pulmonary stenosis and a ventricular septal defect, and 2 with patent ductus arteriosus. All 3 of our cases had localized situs inversus of the ventricles and coronary arteries, and interventricular septal defects, while 2 also had patent ductus arteriosus and preductal coarctation of the aorta, and 1 had a malformed left atrioventricular valve.

EMBRYOLOGY

Although a great deal has been written about the embryologic basis of corrected transposition, no agreement has been reached. Spitzer[2] believes that in "uncorrected" transposition, the bulboventricular loop of the embryonic heart does not go through the normal amount of torsion. This results in incomplete migration and fusion of both primary bulbar septa, resulting in a reopening of the right ventricular aorta and obliteration of the left. Spitzer feels that the aorta in a corrected transposition is an inverted, reopened right ventricular aorta. Walmsley[3] believes that inversion of the bulboventricular loop explains the features of corrected transposition. Anderson[1] emphasizes that both transposition and inversion of the aorta and pulmonary artery are involved. They are transposed, as the normal anteroposterior relationship between the two vessels is reversed. They are also inverted, because in corrected transposition the aorta arises to the left of the pulmonary artery, while in the normal heart the aorta arises slightly to the right of the pulmonary artery.

CLINICAL FINDINGS

Corrected transposition of the great vessels, per se, does not result in any significant physiologic disturbances or clinical manifestations. However, the associated cardiac anomalies often are of great clinical significance. The diagnosis of the associated anomalies clinically is usually not difficult. Clinical recognition of the corrected transposition itself is more subtle, although there are certain features which may lead to the diagnosis.

There is no significant sex difference in the incidence of corrected transposition; 2 of our 3 cases were male. One of our 3 cases exhibited a precordial bulge. None had a palpable thrill. All had Grade 2 or 3 systolic murmurs along the left sternal border; 2 of the 3 cases had a soft diastolic murmur in the same area.

Anderson emphasizes several consistent electrocardiographic features which he found helpful. The first was A-V block, usually first degree; this was found in none of our 3 cases. He also points out that in normal hearts the usual precordial pattern is rS in Lead V_1 and qR in Lead V_6, while there was a reversal of this pattern in cases of corrected transposition. We found no consistent pattern in Leads V_1 and V_6. Thus, we find no evidence of characteristic electrocardiogram in corrected transposition.

Routine chest roentgenograms in our 3 cases revealed generalized cardiac enlargement. In all cases the pulmonary vascular markings were accentuated. Angiocardiographic studies were performed in 2 of the 3 cases. In the first case these studies revealed, in addition to a ventricular septal defect with a left-to-right shunt, a counterclockwise rotation of the great vessels, with aortic arch to the left of the pulmonary artery. This permitted a clinical diagnosis of corrected transposition in Case 1. Retrospective examination of the angiocardiogram in Case 3 showed that the malformation could have been diagnosed by the same sign if the readers had been alerted to this anomaly at the time. Anderson describes a similar characteristic anteroposterior view of the angiocardiogram, showing the main pulmonary artery located medially and the aorta forming the upper left border of the heart.

Cardiac catheterization was performed in all 3 cases. It did not contribute to the diagnosis of corrected transposition. Anderson points out that the catheter often cannot be passed into the pulmonary artery in corrected transposition, as the right-sided atrioventricular valve lies closely adjacent to the pulmonic valve, making too sharp an angle for passage of the catheter.

Surgical intervention is indicated only for the correction of associated cardiovascular anomalies; corrected transposition itself results in no physiologic disturbance requiring correction. However, it is very helpful for the surgeon to have preoperative knowledge of the anomalous position of the great vessels and coronary arteries. In 2 of our cases, surgery was directed to the correction of the patent ductus arteriosus and coarctation of the aorta. In the third case, the interventricular septal defect was repaired surgically.

Wiland[4] has emphasized the rarity of extracardiac congenital anomalies associated with "uncorrected" complete transposition of the great vessels. One of our 3 cases of corrected transposition exhibited an extracardiac anomaly—an intravesical stenosis of the left ureter, with an associated hydroureter and hydronephrosis. A second case had a bile-stained, cirrhotic liver; however, the changes were interpreted as those of congestive cirrhosis. No abnormality in the biliary tree was found.

In the experience of Indiana University Medical Center, attempts to repair the triple anomaly of combined coarctation of the aorta, patent ductus arteriosus, and interventricular septal defect have carried an almost uniformly poor prognosis, whether or not there is an associated corrected transposition of the great vessels. Surgical experience indicates that the additional anomaly of corrected transposition of the great vessels does not alter the prognosis in the surgical repair of simple interventricular septal defects.

CASE REPORTS

CASE 1.—N. P. was referred to the Indiana University Medical Center at the age of 4 months because of difficult respirations. He had apparently been well until 3 weeks prior to admission, when he developed tachypnea and wheezing, with a temperature of 104° F.

Physical examination revealed a well-developed, well-nourished infant. The upper respiratory tract was clear. The chest showed a precordial bulge with intercostal retraction. There was a Grade 3 systolic murmur, heard loudest at the fourth left intercostal space, and a short rough presystolic murmur in the same area. There were coarse râles audible in both lungs. Both the spleen and liver were palpable about 1 to 2 cm. below the costal margins. There was no peripheral edema or cyanosis.

Electrocardiographic studies revealed sinus tachycardia. Cardiac catheterization and selective angiocardiography were performed. These revealed a counterclockwise rotation of the great vessels, with the aortic arch to the left of the pulmonary artery. There was a ventricular septal defect with a left-to-right shunt. A diagnosis of corrected transposition of the great vessels was made.

An attempt was made to close the interventricular septal defect, using the pump oxygenator and open heart surgery. A ventricular septal defect was repaired through the right atrioventricular valve, exposed by right atriotomy. The operation was uneventful. However, about 6 hours postoperatively, the child developed shallow respirations and irregular pulse rate and expired.

Autopsy.—At autopsy the heart was seen to be greatly enlarged, weighing 78 grams (expected weight, 30 grams). The heart measured 59 mm. from base to apex and 60 mm. in transverse diameter. There were hypertrophy and dilatation of both ventricles. The right ventricu-

lar myocardium varied between 6 and 8 mm. in thickness, while the left ventricular myocardium varied between 7 and 8 mm.

The aorta and pulmonary artery were transposed, the aorta arising anterior to and to the left of the pulmonary artery. The vessels coursed upward parallel, without crossing in the usual manner. However, the aorta arose from the left-sided ventricle, and the pulmonary artery from the right-sided ventricle, thus carrying arterial and venous blood, respectively. The ventricles were also inverted. The right-sided ventricle possessed delicate trabeculae carneae. The right-sided atrioventricular valve was bicuspid and had a circumference of 50 mm. The leaflets were anteromedial and posterolateral, the latter arising just inferior to the pulmonic valve. There were two papillary muscles—located on the anterolateral and posterolateral walls. The pulmonic valve was dilated (circumference, 40 mm.); the three cusps were anterior, posterolateral, and posteromedial. There were no pulmonary conus and no crista supraventricularis. There was slight fibrous thickening of the endocardium, especially on the interventricular septum.

The left-sided ventricle had coarse trabeculae carneae. Its atrioventricular valve (circumference, 70 mm.) possessed three leaflets—anteromedial, posteromedial, and lateral. Only one well-formed papillary muscle was present, located on the anterolateral wall of the ventricle. The lateral and posteromedical leaflets were attached directly or by very short, thick chordae, and hence were depressed about half way into the ventricle. There was slight fibrous thickening of the leaflets, especially at the free margins. The aortic valve (circumference, 28 mm.), had three cusps—anterolateral, posterolateral, and medial. The aorta arose from a well-defined conus arteriosus, separated from the remainder of the ventricle by a crista supraventricularis. There was slight fibrous thickening of the endocardium.

There was a high interventricular septal defect, with a diameter of 1 cm. The margins had been approximated surgically. Both atria were dilated. The foramen ovale was patent but partially guarded. All four pulmonary veins drained into the left atrium; the superior and inferior venae cavae and the coronary sinus drained into the right atrium. The ductus arteriosus was not patent.

The coronary arteries were inverted but both arose from the aortic valve. The right coronary artery divided into anterior descending and right circumflex branches.

Microscopic examination of the lungs revealed slight thickening of the walls of the pulmonary arterioles.

CASE 2.—M. S. was a white male infant admitted at the age of 22 days for evaluation of an enlarged heart. No cyanosis or respiratory distress were noted during the first weeks of life. The infant was circumcised at the age of 8 days; a few hours after this he became cyanotic and exhibited labored respirations. Chest x-rays showed cardiac enlargement, and he was referred to the Indiana University Medical Center.

On physical examination, he was not cyanotic; there was slight red mottling of the skin of the trunk. There were moist râles throughout the chest, but no dullness. A precordial bulge was not present. The left border of cardiac dullness was in the left anterior axillary line. The heart sounds were loud and there was a gallop rhythm. There was a Grade 2 systolic murmur, loudest in the third left intercostal space, with some transmission to the left axilla and back. No thrill was palpated. There was definite pretibial and eyelid edema. Peripheral pulses were weak, with radial pulses stronger than the femoral. The liver was palpable at the level of the umbilicus; the spleen was palpable 2 to 3 cm. below the left costal margin.

Electrocardiographic studies revealed a sinus tachycardia with an abnormal QRS-complex over the right ventricle, suggestive of right ventricular hypertrophy.

Radiographic studies revealed marked generalized cardiac enlargement, with definite enlargement of the right ventricle. Cardiac catheterization studies were compatible with a patent ductus arteriosus and a coarctation of the aorta.

When the child reached the age of 5 weeks, thoracotomy was performed. A large ductus arteriosus emptied into the aorta distal to the coarctation. Proximal to this the coarctation extended for a distance of 1.5 cm. The coarctated segment was excised; the ductus was divided at the pulmonic end, which was then anastomosed to the arch of the aorta at the site where the coarcted segment had been transected. The child did well during the surgery and immediately thereafter. However, the following day he was found dead.

Autopsy.—At autopsy the heart was seen to be greatly enlarged, extending almost to the left lateral thoracic wall and a short distance to the right of the mid-sternal line. The heart weighed 56 grams (expected weight, 20 grams). There were hypertrophy and dilatation of both ventricles.

As in Case 1, the aorta and pulmonary artery were transposed, the aorta arising anterior to and to the left of the pulmonary artery; the vessels coursed upward without crossing one another in the usual manner. The pulmonary artery was dilated, with an external diameter twice that of the aorta. However, the aorta arose from the left-sided ventricle, thus carrying arterial blood to the systemic circulation, and the pulmonary artery arose from the right-sided ventricle, carrying venous blood to the lungs. In addition, there was ventricular inversion, with the right-sided ventricle exhibiting morphologic characteristics of a normal left ventricle and vice versa. The right-sided ventricle had fine, delicate trabeculae carneae, and a bicuspid atrioventricular valve.

Fig. 1.—Case 2, showing right-sided ventricle and pulmonic valve. Note the delicate trabeculae carneae and the high interventricular septal defect, through which pass chordae tendineae from the left atrioventricular valve.

The left-sided ventricle had coarse trabeculae carneae, a tricuspid atrioventricular valve, and a well-defined conus arteriosus. The delicate chordae tendineae were attached to three papillary muscles; two were on the lateral walls of this ventricle, one anteriorly and one posteriorly. The third papillary muscle, with chordae extending to the anterior and posteromedial leaflets, was displaced onto the lateral wall of the right-sided ventricle, so that the chordae passed through a high, membranous interventricular septal defect, which measured 10 by 13 mm.

The right atrium, into which drained the systemic veins, was much larger than the left atrium, into which drained the pulmonary veins. The coronary arteries were inverted. The right-sided coronary artery divided into anterior descending and right circumflex branches.

At the site of the resected preductal coarctation, the anastomosis between the aortic arch, just distal to the left subclavian artery, and the divided proximal end of the ductus arteriosus, was intact and partially occluded by a mural thrombus, thus allowing some arterial blood to flow from the aortic arch through the ductus into the descending aorta.

There was moderate thickening of the walls of the pulmonary arterioles. Recent thromboemboli were seen in several small pulmonary arteries.

CASE 3.—C. E., a white female infant was admitted at the age of 3½ months, with a tentative diagnosis of congenital heart disease. At the age of 2 months she had two episodes of bronchopneumonia. At that time a heart murmur was detected.

On admission she was poorly nourished, breathing rapidly, with occasional high-pitched expiratory noises. The lung fields were clear. There were no precordial bulge and no thrills. There was a Grade 3 systolic murmur, loudest at the apex, but also audible over the precordium and back. There was a soft, medium-pitched diastolic murmur along the left sternal border. The liver and spleen were not palpable. Peripheral pulses were good. There was no cyanosis and no clubbing.

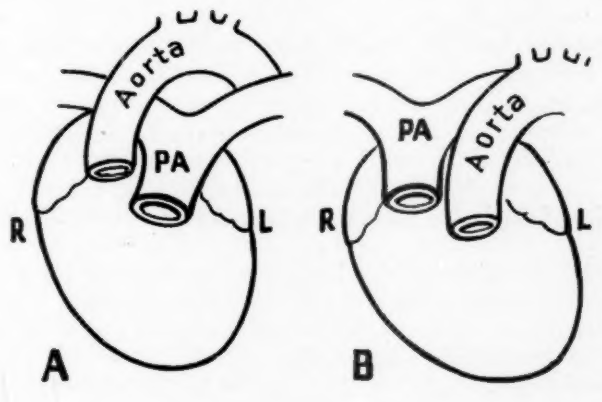

Fig. 2.—Top: *A*, Normal heart, with pulmonary artery arising anterior to and to the left of the aorta. *B*, Corrected transposition, with aorta arising anterior to and to the left of the pulmonary artery. Bottom: Case 2, superoanterior view, showing aorta arising anterior and to the left.

An electrocardiogram revealed a sinus tachycardia, and QRS and S-T segment changes of right ventricular hypertrophy. Chest film suggested enlargement of right and left atrium and right ventricle. The base of the heart was wide. Cardiac catheterization was compatible with ventricular septal defect, showing systemic pressures in the right ventricle. Selective angiocardiography with cineradiography revealed a patent ductus with flow from the pulmonary artery into the aorta.

Thoracotomy was performed under a general anesthetic. When the pericardium was open, the aorta was found anterior to and to the left of the pulmonary artery. A large ductus was present. There was a coarctation proximal to the ductus, which extended for about 1.5 cm. The ductus was ligated and transected. The entire length of the coarctation was excised, with an end-to-end anastomosis. The patient was in fair condition at the end of the surgery, but was found dead that night.

Autopsy.—At autopsy the heart was seen to be enlarged, weighing 63 grams (expected weight, 30 grams). There were hypertrophy and dilatation of the right ventricle.

The aorta and pulmonary artery were transposed, the aorta arising anterior to and to the left of the pulmonary artery. The vessels ascended parallel and did not cross in the usual manner. However, the aorta arose from the left-sided ventricle and carried oxygenated blood; the pulmonary artery arose from the right-sided ventricle and carried venous blood. The ventricles were also inverted. The right-sided ventricle possessed delicate trabeculae carneae and a bicuspid atrioventricular valve, but no crista supraventricularis and no pulmonary conus. The left-sided ventricle had coarse trabeculae carneae, a tricuspid atrioventricular valve, and a conus arteriosus separated from the remainder of the ventricle by a crista supraventricularis.

There was a high interventricular septal defect, measuring 10 by 7 mm. All four pulmonary veins drained into the left atrium. Both venae cavae and the coronary sinus drained into the right atrium.

The coronary arteries were inverted, but both arose from the aortic valve. The right coronary artery divided into anterior descending and right circumflex branches.

The aortic anastomosis, at the site of the resected coarctation, lay distal to the left subclavian artery and proximal to the divided ductus arteriosus.

Microscopic examination revealed no abnormalities in the pulmonary vessels.

SUMMARY

This is a brief review of the clinical and pathologic features of corrected transposition of the great vessels of the heart. In this condition, the aorta and pulmonary artery are transposed, with the aorta lying anterior to the pulmonary artery; however, the aorta arises from the left-sided ventricle and carries oxygenated blood, while the pulmonary artery arises from the right-sided ventricle and carries venous blood. There is usually, also, localized inversion of the ventricles and the coronary arteries. Clinical manifestations result from the frequently associated cardiac anomalies, especially interventricular septal defect.

Three case reports of corrected transposition are presented. These were studied both clinically and at autopsy.

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Routine Electrocardiography: Postprandial T-Wave Changes

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For some years a routine electrocardiogram has been recorded as part of the Royal Canadian Air Force aircrew medical selection program. This procedure has been of considerable value in view of the risk involved and the high cost of pilot training, despite the fact that less than 0.5 per cent of the aircrew applicants are rejected as a result of this electrocardiographic study. Furthermore, it has been our experience that the routine electrocardiogram has, on a number of occasions, brought to light organic lesions overlooked or not readily apparent on the initial clinical examination. Recently, an example of atrial septal defect with minimal clinical findings, which was overlooked on routine induction examination, became apparent because of the findings of incomplete right bundle branch block and right ventricular hypertrophy on the routine electrocardiogram.

In an earlier study of 7,500 routine electrocardiograms, questionable T-wave findings occurred in 240 cases. When further studies were carried out, including cardiovascular assessment, 234 cases were normal or could be explained on the basis of physiologic changes. The remaining 6 cases presented definite cardiovascular abnormalities or continued to show an abnormal electrocardiogram that could not be explained. In the cases in which repeat electrocardiograms were normal, the initial T-wave abnormality could be explained by various environmental factors, such as respiration, posture, and postprandial effects.[1]

It has been shown that "abnormal" T-wave patterns occur in some otherwise normal people following the ingestion of food,[1-5] although in the majority of individuals few or no changes are observed. T-wave changes may occur also as a result of electrolyte changes associated with vomiting, gastrointestinal fistula, diarrhea, etc. Occasionally, a diagnosis of coronary artery disease or myocardial infarction may be made erroneously. A classical example of this (Fig. 1) occurred in a 47-year-old man admitted with a history of indigestion, nausea, vomiting, and upper abdominal distress. Because of the electrocardiographic findings he was considered to have had a recent myocardial infarction, and gastrointestinal investigation was delayed. This case was reviewed

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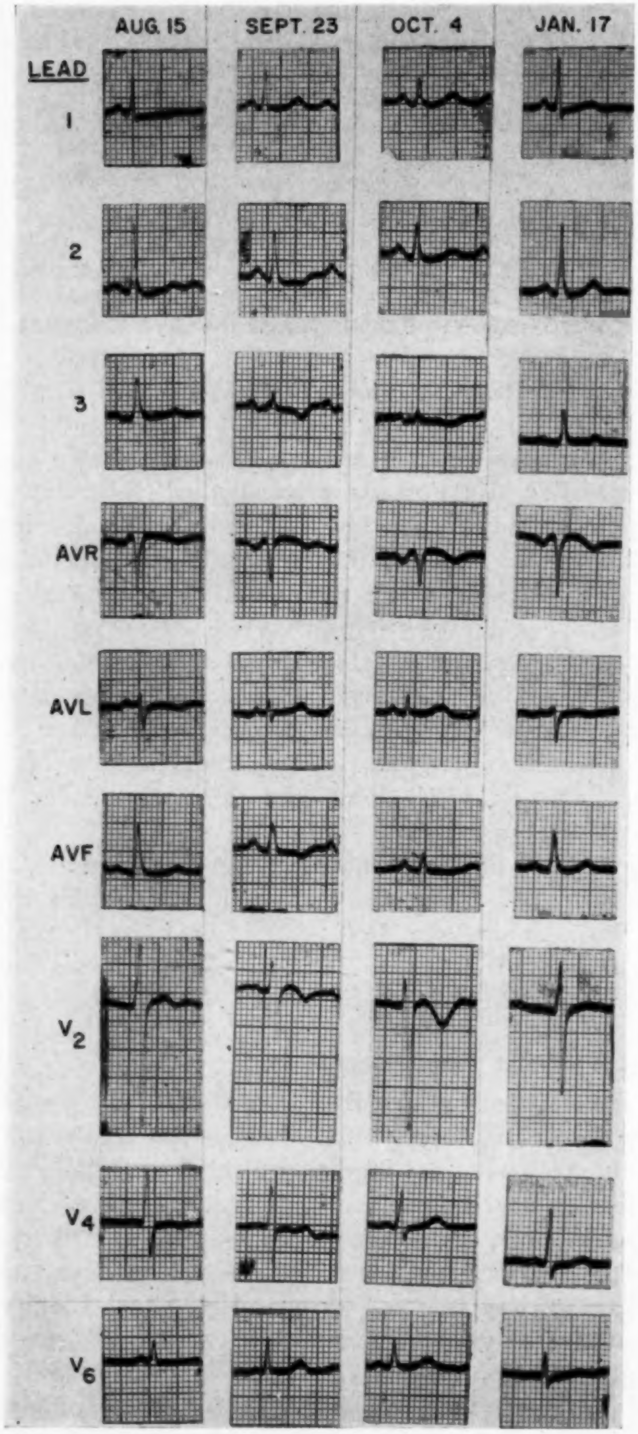
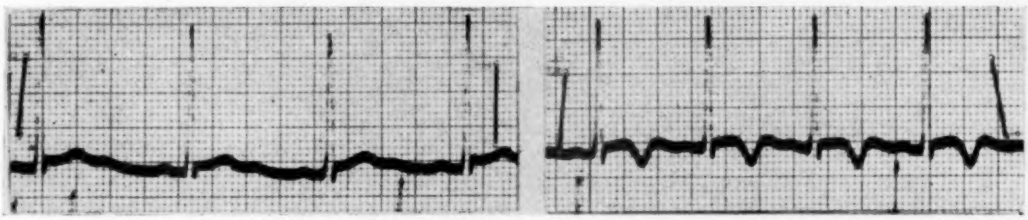


Fig. 1.—Serial electrocardiograms of a 47-year-old white man. Aug. 15: Admission tracing considered initially to be the result of cardiac infarction. Sept. 23: Example of serial tracings showing the changing T-wave pattern. Changes now interpreted as being due to electrolyte shifts. Oct. 4: Tracing obtained immediately following bowel resection for malignant obstruction. Jan. 17: An example of the normal tracing obtained postoperatively.

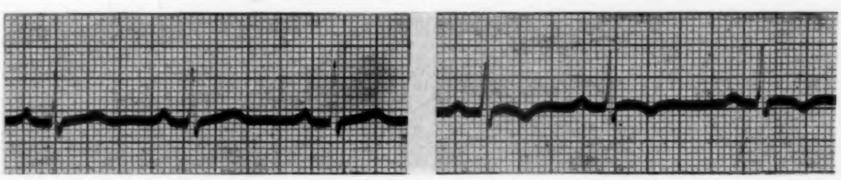
by a cardiologist who felt that the electrocardiographic pattern could be explained on the basis of bowel and electrolyte disturbance. A subsequent barium series revealed a carcinoma of the hepatic flexure, which was removed. The postoperative tracing continued to show T-wave abnormalities, but all subsequent tracings have been normal (Fig. 1).

The effects of exercise, respiration, tachycardia, ingestion of ice water, Adrenalin, potassium, etc., in the production of T-wave abnormalities have been recognized for many years.[6] In our own experience numerous examples of noncoronary T-wave changes have been encountered, both clinically and in our studies with routine electrocardiography in healthy, fit young men (Fig. 2).



A. B.

Fig. 2.—Lead V_4 of a healthy, 18-year-old man before (*A*) and immediately following (*B*) ingestion of ice water.



A. B.

Fig. 3.—Lead II of a healthy, 21-year-old man before (*A*) and one hour following (*B*) ingestion of 100 Gm. of glucose.

Similarly, we have shown "significant" T-wave changes following the ingestion of glucose in completely healthy young men, confirming the work of Rochlin and Edwards[5] (Fig. 3). Since such marked effects as those shown in Figs. 2 and 3 can be produced by ingestion, it is reasonable to expect that many of the so-called T-wave abnormalities encountered in routine electrocardiograms may be postprandial in origin. Consequently, during the recent past all tracings with questionable T-wave findings have been repeated after a period of fasting.

MATERIAL AND METHODS

In this study, electrocardiograms taken on 2,000 consecutive, healthy young men, aged 17 to 24 years, were reviewed. These men had passed a rigid clinical examination prior to aircrew training. In these individuals a routine 13-lead electrocardiogram was recorded in the recumbent position at various times thoroughout the day. All questionable or abnormal tracings were repeated after an overnight fast. Only cases which showed abnormal T waves in the initial tracing, and in which the repeat tracings after fasting were normal, are included in this study.

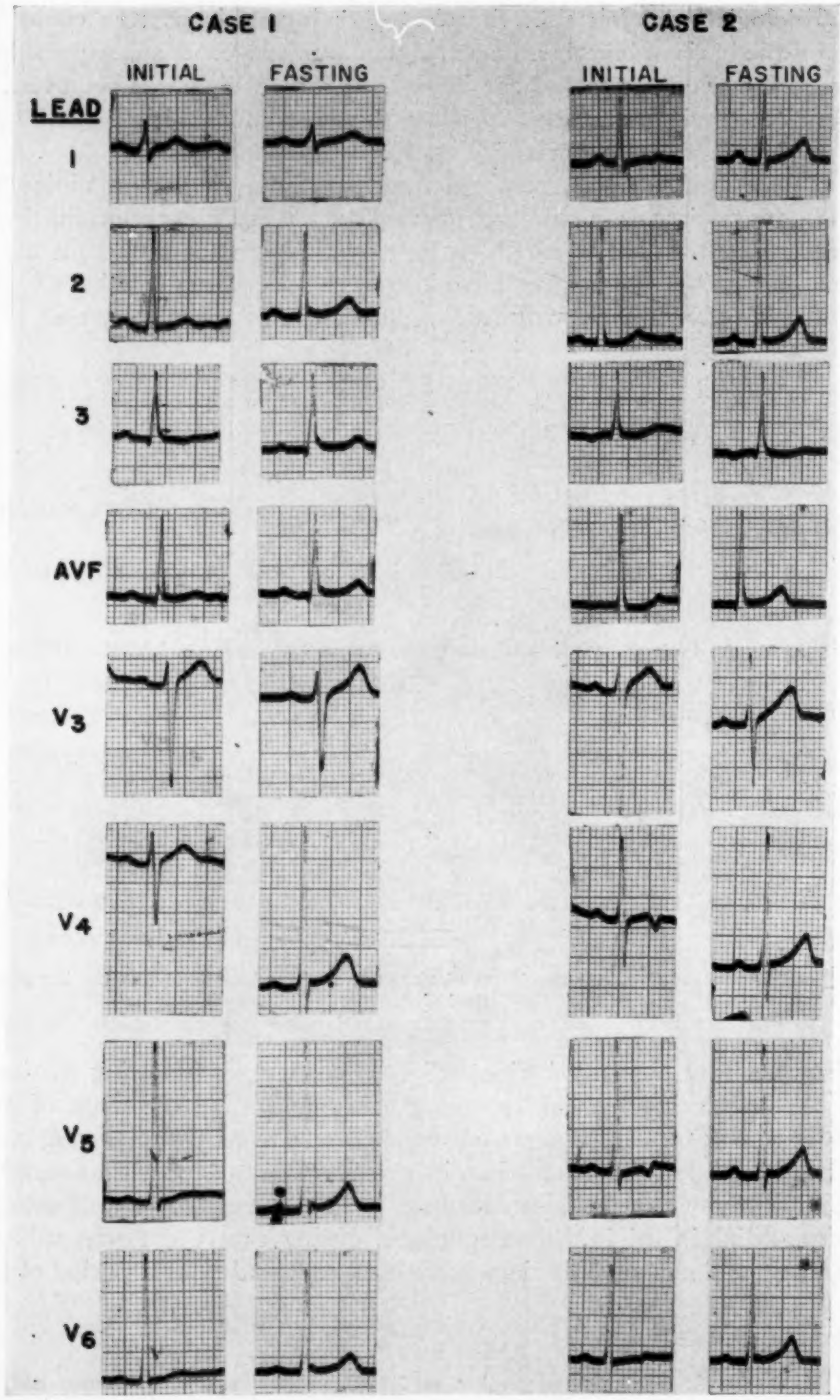


Fig. 4.—Case 1. Fit young man, aged 18 years. Note increased amplitude of T waves, especially in Lead V_4 after fasting. Case 2. Fit young man, aged 17 years. Note change from negative T waves in Leads I, V_4, and V_5 to normal upright T waves after fasting.

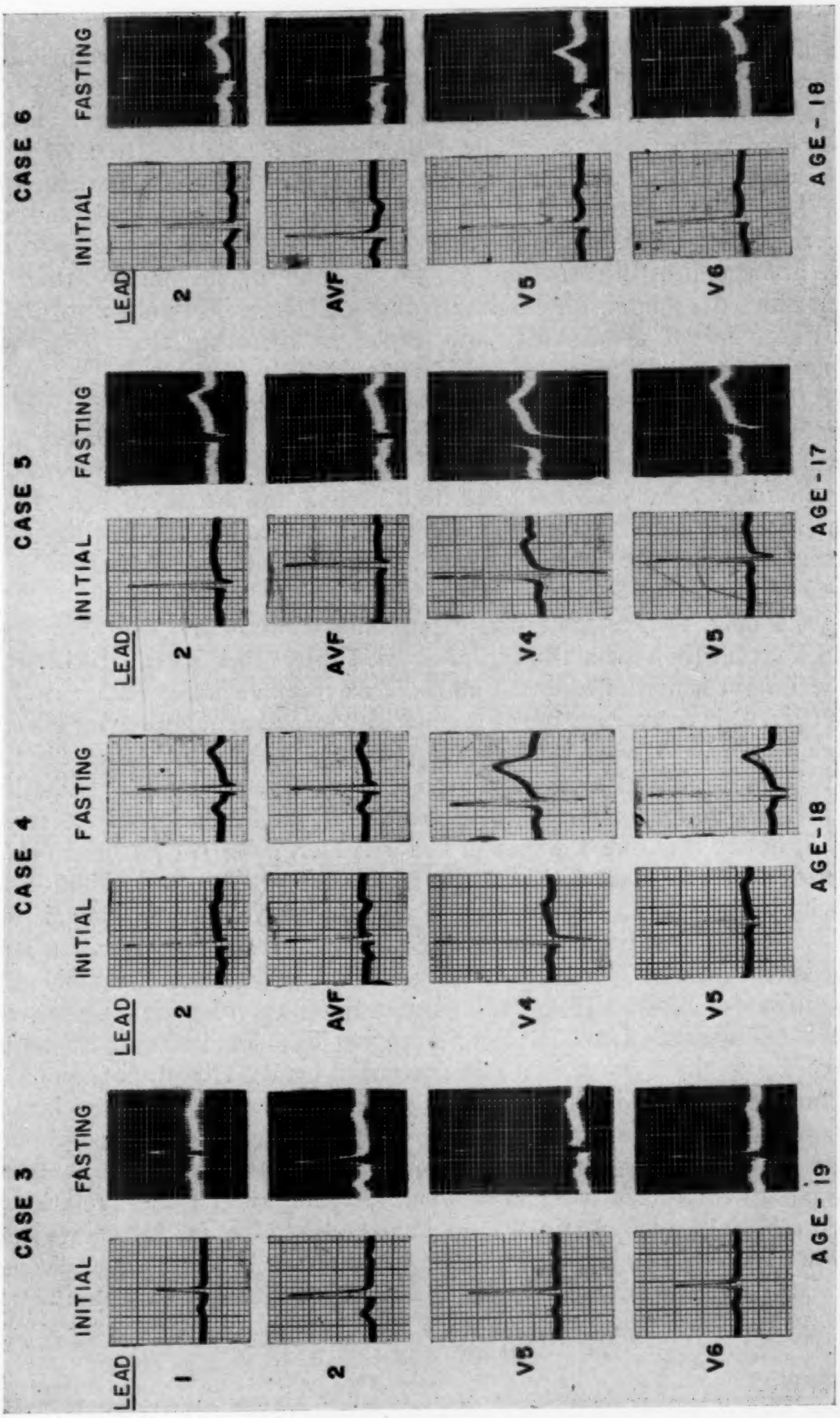


Fig. 5.—Selected electrocardiographic leads from healthy, fit young men, showing abnormal T-wave patterns changing to normal in the fasting state.

RESULTS

Of the 2,000 consecutive routine tracings taken at random throughout the day there were 163 tracings which revealed T-wave abnormalities or variations from the normal. In 85 cases the initial electrocardiographic T-wave variation was not considered to be the result of postprandial change. In all but 3 of these 85 cases the initial electrocardiographic abnormality was explained on a technical or physiological basis other than postprandial change, and these men were passed as fit. In the remaining 3 cases the tracings showed gross T-wave abnormalities which could not be explained; consequently, these men were considered as unfit for aircrew training. The rejection group and the group whose initial abnormality was explained by other than postprandial change will not receive further consideration here.

Of the 78 cases considered to have T-wave changes of a postprandial nature, 29 cases revealed negative T waves in Leads I or II and/or the lateral precordial leads in the initial tracing. The remaining 49 cases revealed flat T waves in the lateral precordial and limb leads in the initial tracing. In both groups (78 cases) the T waves were completely normal in the fasting tracing. Electrocardiograms of 6 cases illustrate the type and degree of T-wave change observed (Figs. 4 and 5).

Case 1 (Fig. 4) presents initially the minor abnormality of a flat T wave in Lead V_4. On the repeat tracing, after the subject had fasted, it will be seen that the T wave is normal and that all the T waves have increased in amplitude. Case 2 (Fig. 4) is representative of the more abnormal type of tracing observed, in which a negative T wave is present in Lead I with negative T waves in Leads V_4 and V_5, in the initial tracing. The repeat tracing, made after the period of fasting, shows perfectly normal T waves and T-wave relationships. In Case 3 (Fig. 5) flat to negative T waves in Leads I, II, V_5, and V_6 become normal in the fasting tracing. Case 4 (Fig. 5) illustrates the problem of isolated T-wave negativity in Lead aV_F. Although the T wave in Lead V_4 is rather low, it would probably be passed as normal, other leads being normal. However, the fasting tracing leaves no room for doubt, because the T waves are all normal and of good amplitude. Case 5 (Fig. 5) illustrates the group of patients observed to have a flat T wave in Lead II with a negative T in Lead aV_F and a terminal negative dip to the T wave in a mid-precordial lead. This tracing would certainly not be accepted initially as normal. However, the repeat tracing, fasting, shows completely normal T waves. Case 6 (Fig. 5) is an example of the final group of tracings seen. Here, a negative or diphasic T wave in Lead II is associated with a negative T in Lead aV_F, with normal T-wave relationships in the precordial leads. Again the tracing recorded after fasting shows normal T waves. It should be emphasized that in all of the 78 cases under discussion the subjects were healthy, fit young men with no associated chronic or acute disease.

DISCUSSION

It has been suggested that alterations in potassium following the ingestion of food is responsible for the postprandial T-wave change.[5] Although no elec-

trolyte studies were carried out in this series, the postprandial lowering of potassium could be a factor in the T-wave changes observed in the cases under discussion. This, however, is an assumption. Such T-wave changes may be unrelated to electrolyte disturbances (Fig. 2). Many of the examples of T-wave negativity supposedly due to glucose, and thus to a postprandial change, are present immediately after the ingestion of glucose and cannot be related to insulin activity and potassium shifts. Similarly, many T-wave changes are also seen as a result of tachycardia, emotional disturbances, and even from drinking a glass of "air." Cardiac rotation and other environmental changes associated with changes in the repolarization process and vector rotation must be considered.[7] In any event, it would appear reasonable to assume that T-wave abnormalities that return to normal in the fasting state are of no pathologic significance in the absence of other findings.

Nonspecific or noncoronary T-wave changes may, of course, be much more misleading in the assessment of routine electrocardiograms in the older age groups for insurance or other purposes. It was apparent from Fig. 1 that T-wave changes may be interpreted as indicating myocardial pathology where none exists. Consequently, in any case, whether routine or diagnostic, in which negative or flat T-wave changes are encountered as the only abnormality, a repeat tracing, after fasting, should be taken.

One further point deserves consideration. Could the postprandial T waves under discussion be indicative of an underlying abnormality, since only 3.9 per cent of individuals, on a random basis, reveal such changes? Although long-term follow-up studies may alter our view, the evidence at the present time supports the opinion that such changes are of no pathologic significance.

SUMMARY

1. In 2,000 consecutive routine electrocardiograms recorded at random throughout the day in healthy, fit men (aged 17 to 24 years) postprandial T-wave changes occurred in 78 cases, or 3.9 per cent.

2. Whenever questionable T-wave findings are present in either routine or diagnostic tracings, a repeat tracing should be recorded in the fasting state.

3. The present evidence supports the view that isolated postprandial T-wave changes are of no pathologic significance.

4. Consideration should be given to the recording of the electrocardiogram in the fasting state wherever possible, particularly when tracings are recorded in connection with routine medical examination.

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The Effect of Nicotinic Acid, Phenyl-Ethyl-Acetamide, and a Combination of Both Drugs on Hypercholesterolemic Dogs and Human Beings

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Recently, Comesaña, Nava and collaborators[1] reported the hypocholesterolemic effect of nicotinic acid—an effect which had already been observed by Sodi-Pallares,[2] in 1955, in patients treated with this drug. Altschul and Herman[3,10] also reported this effect in a study with rabbits and in a small group of normal human subjects.

Our earlier communication showed the rapid hypocholesterolemic action of nicotinic acid, as well as the potentiating action of phenyl-ethyl-acetamide when it was administered simultaneously with nicotinic acid to normal animals.

The daily increasing interest in the search for drugs which can lower blood cholesterol and can be used routinely in the treatment of arteriosclerosis has intensified the study of new drugs; among the latter, sitosterol,[4] 4-cholestanone,[5] and phenyl-ethyl-acetamide[6,7] have been most investigated.

Nevertheless, Nava and Comesaña[8] have noted that for the systematic pharmacologic study it is necessary to experiment not only with normal animals but also with others which simulate the changes observed in the clinic, since some drugs do not act on normal subjects, but do have an effect in pathologic conditions. This concept prompted us to study the action of nicotinic acid, phenyl-ethyl-acetamide, and a combination of the two, not only in normal dogs but also in others with high-cholesterol diets and with high plasma-cholesterol levels. In addition, the action of these drugs was studied in 40 patients with cardiovascular derangements and concomitant hypercholesterolemia.

It is important to note that our experiments suggest that the combination of nicotinic acid and phenyl-ethyl-acetamide will come to occupy a prominent place among hypocholesterolemic drugs, since in combination they provide one drug which has an immediate action and another with a prolonged action.

In order to produce significant decreases in blood cholesterol, it is necessary to administer phenyl-ethyl-acetamide for more than 6 to 8 weeks. The decreases achieved vary between 6.7 and 10 per cent. Phenyl-ethyl-acetamide acts by inhibiting the synthesis of cholesterol.[9]

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The drug 4-cholestanone, which reduces the capacity of the liver to convert acetate into cholesterol,[5] has the disadvantage of inducing arteriosclerosis in dogs and rabbits when it is administered for a long time.

Sitosterol produces hypocholesterolemia only when it is administered continuously for 30 to 45 days.[4] This drug decreases the absorption of cholesterol in the digestive apparatus.

Nicotinic acid at a dosage of 50 mg. daily produces a decrease in cholesterol which is 26 per cent on the first day and 21 per cent on the fourth day, while with phenyl-ethyl-acetamide the levels of cholesterol decrease by only 4 to 14 per cent during the first days.[1]

The combination of nicotinic acid and phenyl-ethyl-acetamide decreases the cholesterol values by 49 per cent on the first day and 47 per cent on the fourth day.[1] The experiments were carried out on dogs with normal levels of cholesterol. The present studies were undertaken to investigate the effect of the drugs on dogs with diets and blood levels high in cholesterol, as well as on a group of cardiovascular patients with hypercholesterolemia. At present we do not know the pharmacodynamic action of nicotinic acid.

METHOD OF STUDY

Dogs.—The experiments were carried out on male dogs varying in weight between 16 and 20 kilograms. A first control group was given the usual diet. A second control group was fed twice daily—once in the afternoon with the normal diet of the first control group, and once in the morning with 3 Gm. of cholesterol suspended in 40 ml. of sesame oil administered orally, with French bread ("bolillo") as the vehicle. A third group of animals was given the same diet as that of the second control group, plus the drugs being studied. This last group was divided into three lots. The first lot was given 100 mg. of nicotinic acid orally, daily for 4 days with some dogs and for 12 days with others, as reported in Fig. 1. The second lot, once high blood-cholesterol levels had been reached, received 400 mg. of phenyl-ethyl-acetamide daily for 8 days (Fig. 2). The third lot, when high blood-cholesterol levels had been reached, received 100 mg. of nicotinic acid and 400 mg. of phenyl-ethyl-acetamide orally, daily for 9 days (Fig. 3).

In these lots it was hoped to obtain high levels of plasma cholesterol, and, generally, they were achieved within 7 to 15 days, as is shown in the results. At the end of this time, the drugs being studied were administered, and the high-cholesterol diet was continued during the period of administration of the drugs. Once the action of the drugs under study was observed, their administration was stopped, the high-cholesterol diet was continued 3 or 4 days, and then suspended and replaced by the normal diet.

The total and esterified cholesterol of the plasma was determined. In some cases the samples were taken daily, and in others every other day during the course of the experiment with the drugs, and for 5 or 6 days after suspension of the high-cholesterol diet. The cholesterol was determined by the method of Bloor.

Cardiovascular Patients.—We used a group of patients with blood-cholesterol values (Bloor method) greater than 200 mg. per cent; in the majority of cases the values were greater than 300 mg. per cent. All had clinical manifestations of coronary, cerebral, or peripheral arteriosclerosis; some were also hypertensive and/or diabetic. Nicotinic acid was prescribed in oral doses of 100 mg. after each meal, i.e., 300 mg. daily. For those who complained of "flushing" or pruritis, the 300 mg. were given in 6 doses of 50 mg. each. Fifteen of the patients with cholesterol figures greater than 300 mg. per cent had been tested previously for periods which varied between 1 and 6 months on a diet low in cholesterol and associated fats, without having obtained appreciable changes in the cholesterolemia. In none of the patients was there any modification of the dietary regimen which had been followed previously during the test period and during the 2 to 4 weeks of postcontrol. The administration of nicotinic acid in the form indicated was

followed in all patients during a minimum of 2 weeks and a maximum of 1 month. After determination of total cholesterol at the end of the aforementioned period, the administration of nicotinic acid was suspended, and at the end of another 2 to 4 weeks, the determination of cholesterol was repeated as a postcontrol test.

EXPERIMENTAL RESULTS

Fig. 1 shows the values for total, free, and esterified cholesterol for the lot of animals which received orally 100 mg. of nicotinic acid. From this figure it can be seen that the high-cholesterol diet increased considerably the blood-cholesterol levels. In the case of Dogs 1, 2, and 3, the high-cholesterol diet was administered for 15 days, and for Dog 4, for 10 days; at the end of this time

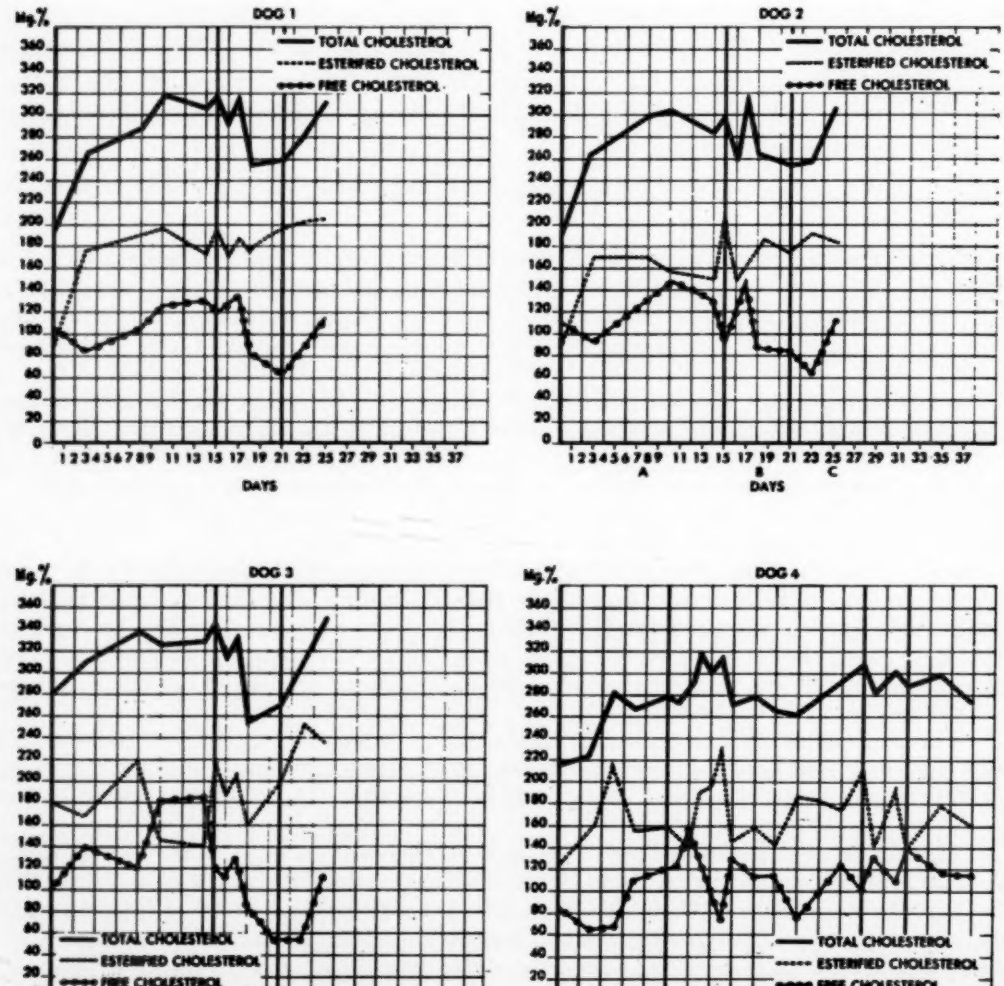

Fig. 1.—Values for cholesterol obtained in the dogs which received 100 mg. of nicotinic acid alone. In this and subsequent figures, *A* = high-cholesterol diet; *B* = high-cholesterol diet and drugs; *C* = high-cholesterol diet without drugs; and *D* = normal diet.

the nicotinic acid was administered. The nicotinic acid produced a drop in blood cholesterol in 3 of the 4 dogs, a drop which was apparent within 24 hours after beginning the treatment. When the nicotinic acid was stopped and the high-cholesterol diet continued, the serum-cholesterol level again increased. In the case of Dog 4 the results were favorable but less notable than in the first 3 animals.

In Fig. 2 are shown the levels of total, free, and esterified cholesterol in dogs which were given 400 mg. of phenyl-ethyl-acetamide alone. This drug produced a slower fall in the level of total cholesterol, but the effect was greater and more prolonged.

The levels of cholesterol obtained in the dogs which received 100 mg. of nicotinic acid and 400 mg. of phenyl-ethyl-acetamide orally, daily, are shown in Fig. 3. It can be seen that the diet high in cholesterol raised the blood-cholesterol

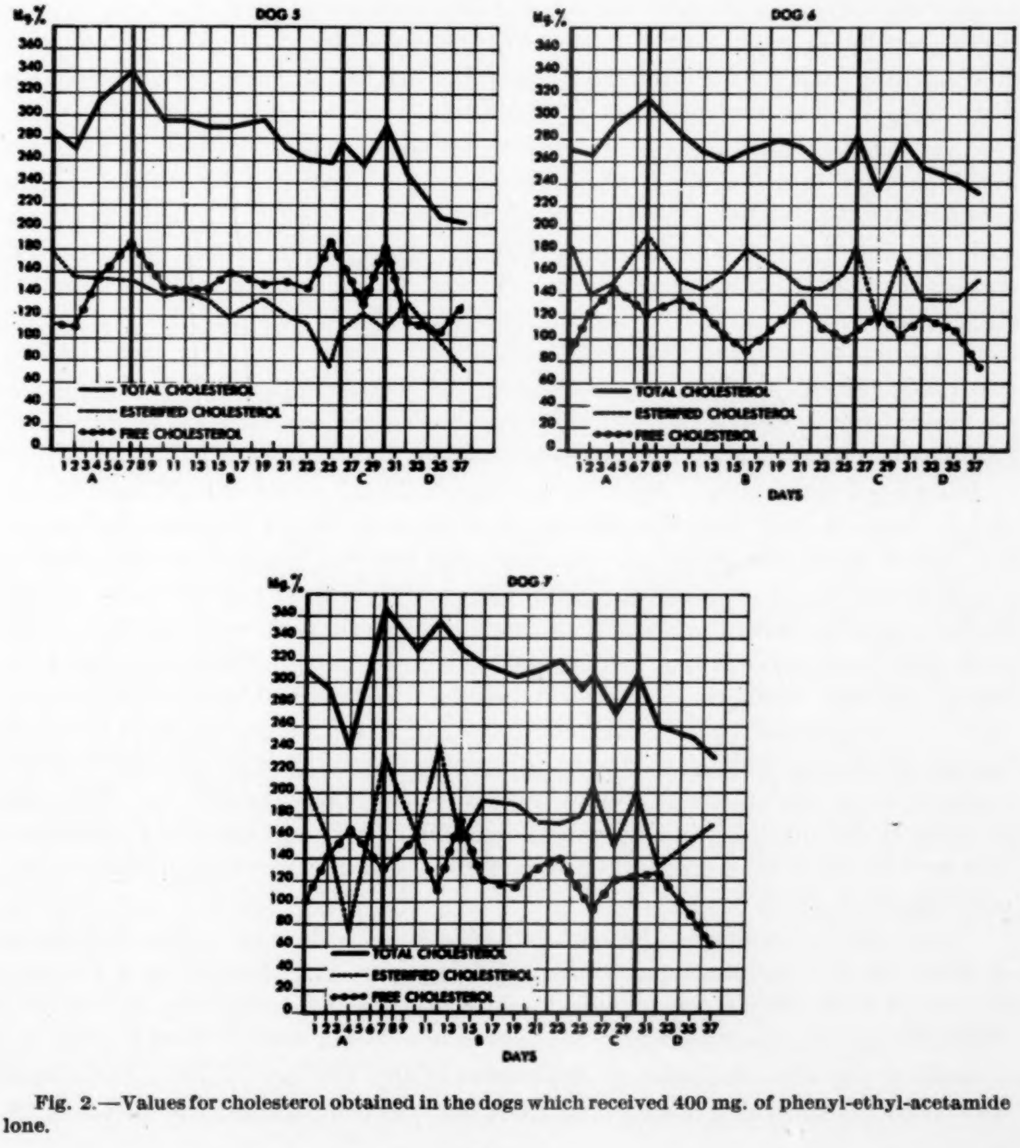

Fig. 2.—Values for cholesterol obtained in the dogs which received 400 mg. of phenyl-ethyl-acetamide lone.

level, and that the administration of the drugs produced a decrease, notwithstanding the continuance of the high-cholesterol diet.

The decrease in the serum-cholesterol levels produced by the combination of nicotinic acid and phenyl-ethyl-acetamide was greater and more sustained than that produced when the two drugs were administered separately. When the drugs were withheld, the cholesterol level rose again; it returned to normal values when the normal diet was resumed.

EFFECT OF THE DRUGS ON THE DIFFERENT FRACTIONS OF CHOLESTEROL

In Dog 1 (Fig. 1), the total cholesterol increased with the diet from 195 to 320 mg. Administration of nicotinic acid produced a maximum decrease to 255 mg. On withholding the drug, the cholesterol again rose to values of 315 mg. In this experiment a marked decrease in free cholesterol was observed, with a curve resembling that of total cholesterol; the esterified cholesterol values were modified but little by the drug, in spite of the marked increase produced by the diet. Similar results were obtained with Dogs 2 and 3.

Fig. 2 shows the values for total, free, and esterified cholesterol for the dogs in which the effect of phenyl-ethyl-acetamide was studied. An example of the results obtained is shown by the curves for Dog 5. The total cholesterol rose with the diet from 285 to 340 mg., and the drug produced a decrease to 260 mg. after about 19 days of treatment; 4 days after suspension of the drug the cholesterol again returned to values of 292 mg. The esterified cholesterol underwent a decrease similar to that produced on the total cholesterol by phenyl-ethyl-acetamide, while the changes produced on the free cholesterol were of little importance. In the case of Dog 6, administration of the drug produced an important decrease in the total cholesterol and there were fluctuations in the value of free and esterified cholesterol. Again in the case of Dog 7, a decrease in total cholestrol is observed, and there is a similar decrease in esterified and free cholesterol.

Fig. 3 shows the curves of total, free, and esterified cholesterol for the dogs in which the combination of nicotinic acid and phenyl-ethyl-acetamide, as well as the variations with the normal and high-cholesterol diets were studied. The most significant curve is that of Dog 10. With the diet the cholesterol rose from 262 to 330 mg. With the combination of nicotinic acid and phyenl-ethyl-acetamide the cholesterol levels decreased to less than the control values, i.e., to 240 mg. on about the fourteenth day of administration of the compounds; when the drugs were withheld there was a new increase in cholesterol to 328 mg. Attention is called to the fact that in this experiment the decrease in esterified cholesterol was greater than that of the free cholesterol, and the same was shown very conclusively in Dogs 8 and 9.

The clinical results can be seen in Table I. The average of the determinations of the control cholesterol was 363.4 mg. per cent; after 2 to 4 weeks of treatment with 300 mg. of nicotinic acid daily, the average decreased to 234.9 mg., i.e., an average decrease of 35.3 per cent. From 2 to 4 weeks after suspension of the administration of cholesterol in the 15 cases in which the control was repeated, the value returned to 335.4 mg. per cent, almost the initial figure.

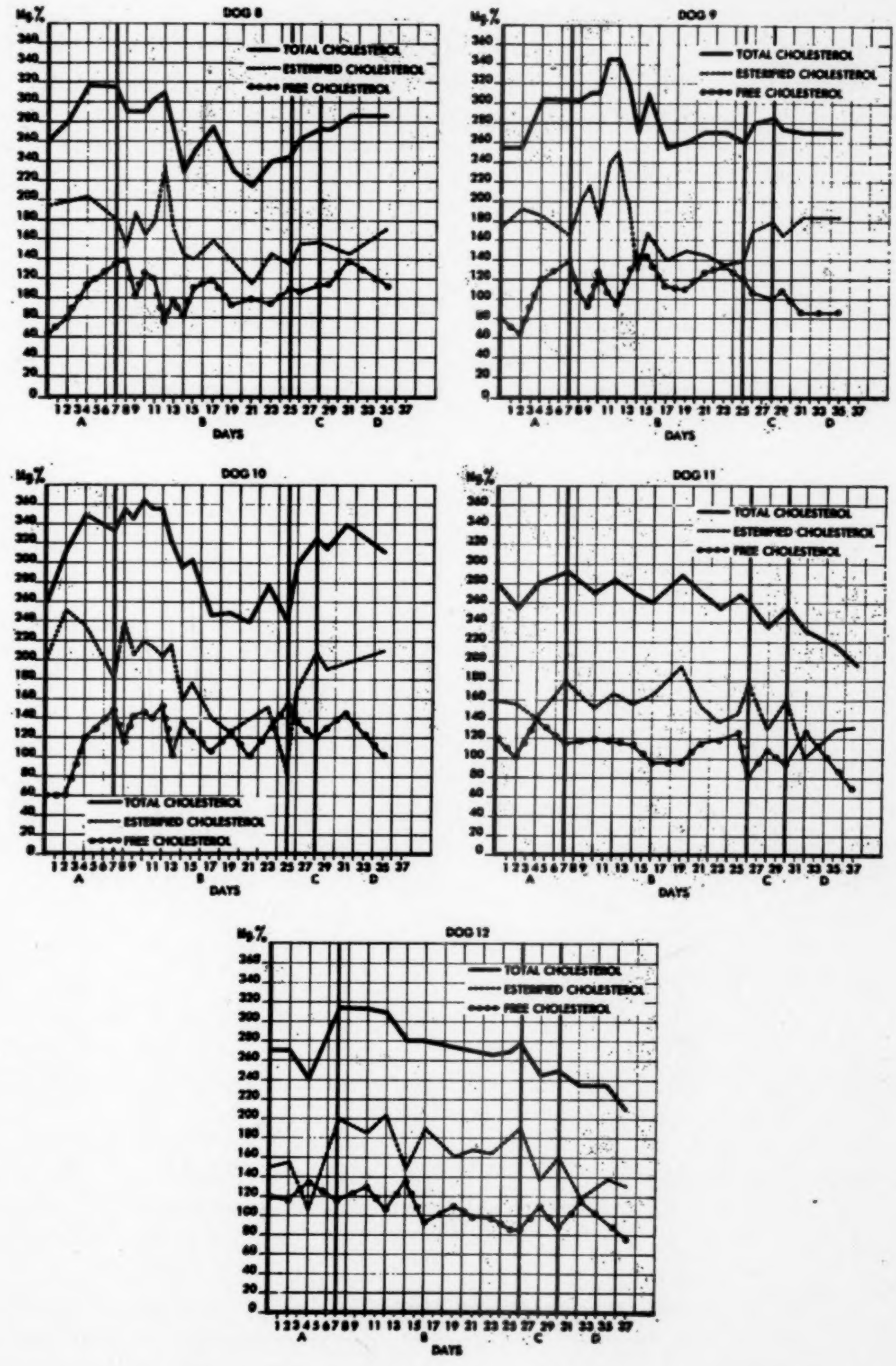

Fig. 3.—Values for cholesterol obtained in the dogs which received 100 mg. of nicotinic acid and 400 mg. of phenyl-ethyl-acetamide in combination.

It can be observed also that, in general, there was a more intense hypocholesterolemic effect in the cases with higher control figures, while those in which the cholesterol was only slightly higher than normal showed almost no significant decrease. Nevertheless, the results are neither proportional nor predictable, since cases with similar control values showed extraordinary decreases (as much as 68 per cent), while other decreases were modest or slight.

TABLE I. CHOLESTEROL IN BLOOD (MG. PER CENT)

CASE	CONTROL	2 TO 4 WKS. WITH NICOTINIC ACID	PER CENT OF VARIATION	2 TO 4 WKS. AFTER NICOTINIC ACID WAS WITHDRAWN
1.	727	412	−43.3	—
2.	515	323	−37.2	—
3.	480	150	−68.7	450
4.	446	293	−33.1	406
5.	436	255	−41.5	355
6.	412	227	−44.9	—
7.	410	220	−45.8	346
8.	410	146	−64.3	—
9.	410	212	−43.3	420
10.	388	261	−32.7	—
11.	377	205	−45.6	390
12.	364	243	−33.2	360
13.	350	247	−29.4	—
14.	350	285	−18.5	341
15.	345	232	−32.7	268
16.	328	208	−36.5	285
17.	325	191	−41.2	—
18.	323	281	−13.0	350
19.	320	180	−43.7	—
20.	320	250	−21.8	—
21.	320	188	−41.2	323
22.	316	202	−39.2	—
23.	312	300	− 4.0	—
24.	308	240	−22.0	305
25.	295	273	− 7.4	—
26.	288	150	−47.9	190
27.	288	182	−36.8	243
28.	277	258	− 6.8	—
29.	252	241	− 4.3	—
30.	212	215	− 1.4	—
Mean values:	363.4	234.9	−35.3	335.4

TABLE II. CHOLESTEROL IN BLOOD (MG. PER CENT)

CASE	CONTROL	WEEKS					
		1ST	2ND	3RD	4TH	5TH	6TH
1.	325	300	276	—	213	—	205
2.	304	273	380	—	233	—	204
3.	278	—	—	233	—	—	198
4.	271	—	260	—	205	—	175

At present we are treating a group of patients with 300 mg. of nicotinic acid and 2.4 Gm. of phenyl-ethyl-acetamide daily, in three doses. Now we report only 4 cases (Table II), but in future communications we will give the results of a more extensive investigation.

DISCUSSION

The experimental data show that both nicotinic acid and phenyl-ethyl-acetamide, alone or combined, have a hypocholesterolemic action in dogs with high levels of cholesterol which have been produced by high-cholesterol diets.

Nicotinic acid in these animals had a rapid hypocholesterolemic action, the levels of cholesterol decreasing after the first dose and the effect being maintained during the administration of the drug, with the low levels of cholesterol continuing in spite of a high-cholesterol diet. The same hypocholesterolemic action was observed in cardiovascular patients with high levels of blood cholesterol (Table I).

Nicotinic acid alone produced a rapid hypocholesterolemic action in 3 of 4 animals studied. The decrease was important after the third day from the beginning of treatment, and it is interesting to note that in the animals with a favorable response, the control figures after the diet were higher than in the 2 animals without favorable response to the drug.

Phenyl-ethyl-acetamide lowered the levels of cholesterol in the 3 animals studied. The decrease, although less marked than that produced by nicotinic acid, was important and sustained, and began on the first day of treatment.

The combination of nicotinic acid and phenyl-ethyl-acetamide was very favorable in the 5 animals studied, returning the levels of cholesterol almost to the control values in all cases. The effect appeared to be sustained and became more apparent on the fifth and seventh days of treatment. The effect was more powerful than that obtained when the drugs were administered separately.

It is interesting to note what happens to the cholesterol levels when administration of the drug is suspended and the hypercholesterolemic diet is continued: (1) In the case of nicotinic acid it was observed that in the animals in which the effect was favorable, with an important decrease in blood cholesterol, the cholesterol values rose on the day following suspension of the drug and reached the high levels of the postcontrol period on the second day. (2) Upon suspension of the phenyl-ethyl-acetamide, the cholesterol level remained low the first day and began to rise on the second day, but the levels were lower than those obtained in the second control period; it would be of greatest importance to study the action of this drug for a longer time. (3) The action of the combination of nicotinic acid and phenyl-ethyl-acetamide was maintained for 2 days after its administration was discontinued, the levels of cholesterol remaining as low as in the first control period before the diet was begun. In only 1 animal did the levels rise when the administration of the combined drugs was stopped.

Satisfactory results were achieved in the animals with daily doses of 100 mg. of nicotinic acid and 400 mg. of phenyl-ethyl-acetamide. Since satisfactory results were obtained in man with doses of 400 to 600 mg. of nicotinic acid and

1,600 to 2,000 mg. of phenyl-ethyl-acetamide daily, we believe to be excessive the doses of 3 to 6 Gm. of nicotinic acid daily which were administered by Parsons and Flinn.[11,12]

The high doses of nicotinic acid used by the authors cited above are not only excessive but can be dangerous, since Nitulescu[13] obtained hyperplastic thyroids in rabbits with doses greater than 15 mg. per kilogram of body weight. Thus can be seen the convenience of using the combination of nicotinic acid and phenyl-ethyl-acetamide, since, when these are used in association, their effects are greater than when they are used separately.

SUMMARY

1. The effect of nicotinic acid alone and in combination with phenyl-ethyl-acetamide on plasma-cholesterol levels was studied in dogs with induced hypercholesterolemia and in arteriosclerotic patients with hypercholesterolemia.

2. In the dogs, nicotinic acid produced a rapid fall in levels of serum cholesterol, and its effect was maintained during the period of administration of the drug. Phenyl-ethyl-acetamide alone lowered the cholesterol values less rapidly, but its effect was more prolonged.

3. In dogs with induced hypercholesterolemia, the combination of nicotinic acid and phenyl-ethyl-acetamide provoked a decrease in cholesterol levels which was more rapid and more prolonged than that produced by the drugs given separately.

4. Nicotinic acid produced a significant decrease in the serum cholesterol of 30 patients with coronary, cerebral, or peripheral arteriosclerosis, in whom the cholesterol values were greater than 300 mg. per cent in the majority of cases. The average decrease produced by nicotinic acid was 35.3 per cent between the second and fourth weeks of its administration.

5. The combination of nicotinic acid and phenyl-ethyl-acetamide decreased the cholesterol values in patients with arteriosclerosis and hypercholesterolemia, thereby confirming the pharmacologic experiments.

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Second Degree Heart Block With Wenckebach Phenomenon: Its Occurrence Over a Period of Several Years in a Young Healthy Adult

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First degree auriculoventricular block is a common electrocardiographic finding. Many causes have been listed for its etiology. In a normal individual, first degree block very frequently is due to increased vagal tone, caused by fatigue in the conducting system as the result of (1) tachycardia, (2) digitalis medication, and (3) inflammatory, toxic, degenerative, or vascular processes that affect the heart.[1]

Second degree auriculoventricular block is much less common, and its occurrence is almost universally associated with either organic disease or digitalis intoxication.

The following is the report of a case of second degree heart block with a Wenckebach phenomenon that has been present over a period of at least 6 years. This has occurred in a patient who has exhibited no evidence of cardiac disease.

CASE REPORT

This 22-year-old man was first seen in January, 1952. He had chest pain of the anterior wall of 3 weeks' duration. The pain was constantly present, but was worse on deep inspiration. There was no history of fever, sore throat, or joint involvement. There was no previous history of any cardiac disability, particularly of rheumatic infection.

Physical examination showed a thin, moderately well-developed man in no distress. His temperature was 98°F. The pulse was irregular and the rate averaged 54 per minute. Blood pressure was 108/60 mm. Hg. No heart murmurs were heard. An electrocardiogram showed a second degree auriculoventricular block with Wenckebach phenomenon.

On the following day a second electrocardiogram was unchanged. The white blood count and sedimentation rate were normal. Fluoroscopic examination of the heart and chest was within normal limits.

He was seen 10 days later, and at this time his heart beat was regular. However, the P-R interval was 0.24 second. During this interval the patient had felt well and had remained at home. Three weeks after he had first been seen it was noted that his heart was again irregular. An electrocardiogram at this time showed that the second degree heart block had returned. On this visit the patient was given atropine, 1/75 of a grain hypodermically. Electrocardiograms were made every 15 minutes. Within 30 minutes the block had reverted from second degree to first degree, with a P-R interval of 0.24 second. The heart rate showed a moderate increase.

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After 1 hour all evidence of block had disappeared and the P-R interval was 0.19 second. In 2 hours all effect of the atropine had disappeared. The heart rate was much slower and the second degree heart block had returned.

Over the next few months he was seen on several occasions. Two months after his first visit his rhythm was regular. The P-R interval at this time was 0.24 second. Five months after his first visit his electrocardiogram again showed a second degree auriculoventricular block with the Wenckebach phenomenon.

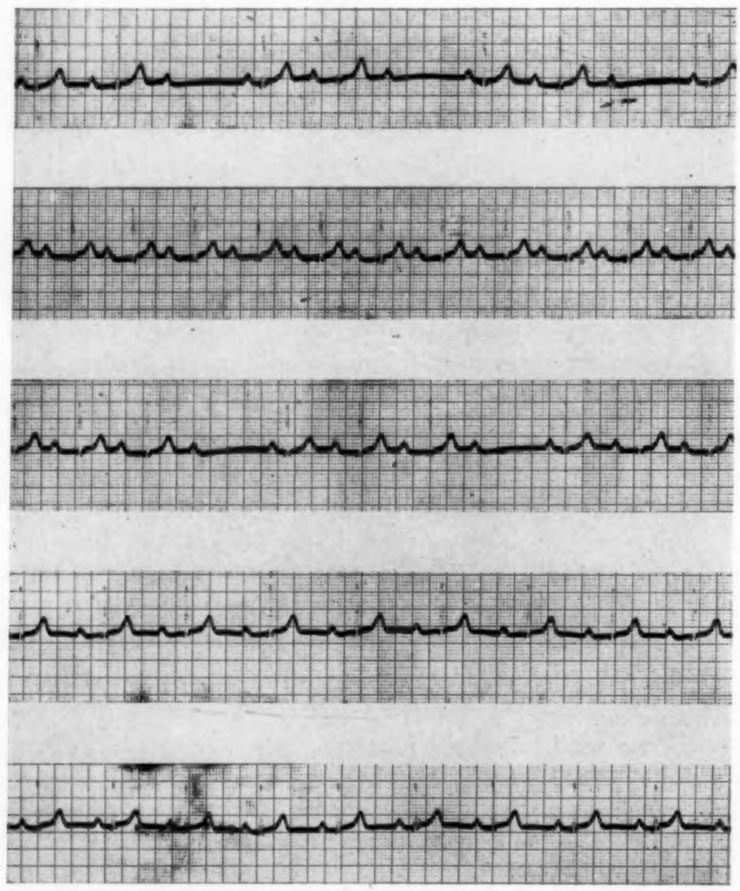

Fig. 1.—*A*, Resting: Second degree auriculoventricular block with Wenckebach phenomenon. *B*, After exercise: First degree auriculoventricular block. Rate is faster. P-R is 0.26 sec. *C*, After left carotid sinus pressure: Second degree heart block returned. *D*, Fifteen minutes after atropine: First degree auriculoventricular block. P-R is 0.28 sec. *E*, Forty minutes after atropine: No block. P-R is 0.18 sec.

After being convinced that he did not have any organic heart disease, the patient was seen only occasionally during the next 5 years. He continued to do rather hard work as the driver of a delivery truck. His hours were long but he experienced no difficulty in handling the job. He noticed from time to time that his heart beat was irregular.

Six years after his first visit he again presented himself for examination. On this occasion he was again found to have a second degree auriculoventricular block with Wenckebach phenomenon. Various tests were done at this time.

Upon exercise there was an increase in the heart rate. The second degree block disappeared. A first degree block with a P-R interval of 0.26 second occurred. Pressure was then applied to

the left carotid sinus and resulted in a return of the second degree block. Drinking cold water failed to increase the block. He was given atropine, 1/50 of a grain hypodermically. Within a period of 15 minutes a first degree auriculoventricular block with a P-R interval of 0.28 second occurred. After 40 minutes the P-R interval decreased to 0.18 second. During this time carotid stimulation had no effect on the P-R interval. Two hours after the atropine was given, its effects had disappeared and the second degree auriculoventricular block had returned (Fig. 1).

DISCUSSION

Impairment in auriculoventricular conduction is very common during the course of acute rheumatic fever. This impairment has been attributed to both increased vagal action and to inflammation of the auriculoventricular node and bundle.[11] Its importance is accentuated by the concept that it indicates active carditis. In general, it is felt that atropine cannot be used to differentiate between the prolongation of the P-R interval caused by vagotonia and that caused by an active carditis. The return to a normal conduction time following the administration of atropine indicates that at least part of the block is of vagal origin. However, the disappearance of auriculoventricular heart block after the use of atropine does not necessarily mean that there may not be a pathologic change, either in the heart muscle or in the conducting system, that is causing the block.[4] Heart block in acute rheumatic fever and other acute infections is often relieved by atropine. Grant[3] noted that atropine regularly restored sinus rhythm in so-called normal subjects with either P-R prolongations or Wenckebach periods. He felt that in all cases of acute rheumatic fever, atropine would produce a normal P-R interval. Other investigators have found cases of acute rheumatic myocarditis with auriculoventricular block that did not respond to atropinization.[5,10] Likewise, chronic, inactive rheumatic heart disease may result in a nonresponsive auriculoventricular block. This is due probably to persistent fibrosis resulting from rheumatic lesions.[12] When the prolonged P-R interval is due principally to widening of the P waves, there is no impaired conduction through the auriculoventricular node and bundle. When heart block, particularly first degree, is due to this type of lesion, it is felt that the change is due to the injury in the auricular myocardium, and no significant alteration can be expected because of changes in the vagus tone.[1,9] Normal conduction is rarely restored by the use of atropine in patients whose difficulty is due to digitalis, arteriosclerotic heart disease, or congenital heart lesions, or in patients with chronic rheumatic myocarditis who have persistent fibrosis of the junctional tissues.

Numerous investigators have reported their experiences in patients with first degree auriculoventricular block. In general, it is caused by rheumatic fever—both the acute and the chronic forms of the disease. However, digitalis and quinidine medication, various infectious processes that involve the myocardium, chronic coronary artery disease, congenital heart disease, and syphilitic heart disease are all acknowledged to be a source of a prolonged P-R interval.[9,14] Many maneuvers, such as tilting, coughing, breath holding, carotid sinus stimulation, as well as the administration of Prostigmin, may cause increase in the P-R interval in cases of acute rheumatic fever.[2-4,6]

While first degree heart block not due to organic disease has been reported,[13] only a very few examples of second degree auriculoventricular block with a

Wenckebach phenomenon have been documented in patients without any evidence of organic heart disease or without drug intoxication. Benedict and Evans[7] reported a case associated with attacks of anxiety, and Levy[8] reported a 14-year-old boy who had no heart disease. In this case the block was lessened by exercise and eliminated by atropine. Breath holding, carotid sinus pressure, and digitalis tended to increase the block.

This man represents a case of marked vagotonia. With the history of chest pain and the second degree heart block occurring in a 22-year-old man, rheumatic fever must certainly be suspected. The fact that no evidence of any active myocardial process or any other infectious process could be found led to the suspicion that this was a case of extreme vagotonia. The follow-up of the patient over a period of 6 years has apparently confirmed the initial impression.

SUMMARY

1. Intermittent second degree auriculoventricular block with the Wenckebach phenomenon has been demonstrated in a patient who does not have organic heart disease. The duration of this phenomenon has been at least 6 years.

2. The effects of atropine and vagal stimulation have been discussed.

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The Normal Spatial QRS-T Angle of the Orthogonal Vectorcardiogram

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Present trends in both electrocardiography and vectorcardiography are toward quantitative data analysis. The spatial QRS-T angle has been proposed by many investigators[1-8] as one means for such evaluations. This criterion indicates the angular relationship between two representative vectors for cardiac activation and recovery. In the past, spatial QRS-T angles have been calculated by many different methods, with varying degrees of accuracy. In the present study, a new method was used which obviates most sources of error of other procedures. Preliminary normal standards for this spatial angle were established in order to serve as a basis for further studies on pathologic series. Schmitt's corrected, orthogonal SVEC-III leads[9] were used. Their enhanced accuracy, as compared to conventional bipolar and unipolar leads, has been demonstrated in torso models[9] and in man.[10]

MATERIAL AND METHODS

Fifty normal subjects were selected at random from a larger group, the latter having been described in more detail in a recent communication.[11] Vectorcardiograms were recorded in the frontal, right sagittal, and horizontal planes, using Schmitt's orthogonal SVEC-III leads.[9] Electronic characteristics of the recording apparatus have been described previously.[10]

The spatial QRS-T angle was determined in the following manner: the area of each planar projection of the QRS loop was measured planimetrically. Then, an axis arising from point E was determined which bisected the area of the QRS loop into two halves (Fig. 1). The time markings of the loops (at intervals of 0.0025 second) were checked against simultaneously recorded scalar orthogonal leads,[10,11] since accurate timing cannot be achieved when vectorcardiograms alone are available. Then, the incidence in time of this "half-area" QRS vector was determined in each plane. The average time from the three plane projections was taken as representative for a mean QRS vector. It has been shown previously[12] that such a mean half-area vector comes very close to the SÂQRS of Ashman and co-workers.[13] The mean angular discrepancy in space between the method described here and that of Ashman was 17° ± 14.3°. Determinations of QRS area from

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scalar leads[13] require considerable enlargements of original tracings in order to keep the repeat variability of the method in reasonable limits. The inherent error of the less time-consuming determinations of mean half-area vectors (17° ± 14.3°) did not exceed the repeat variability of Ashman's method.

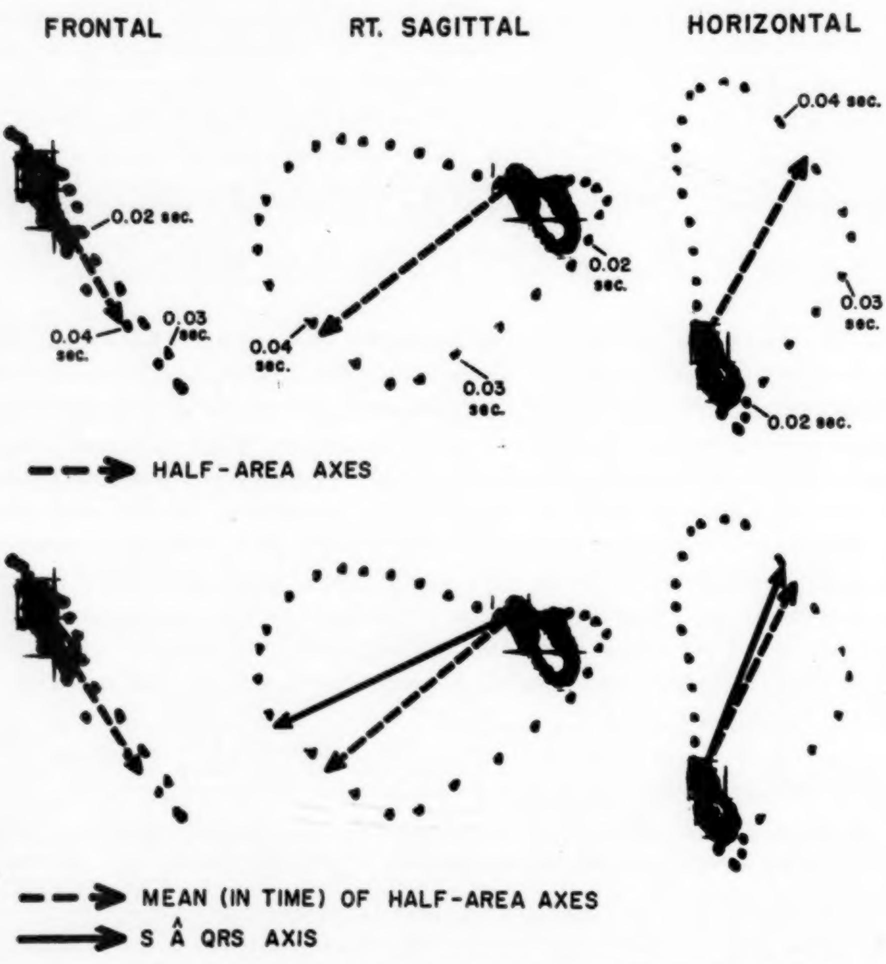

Fig. 1.—The half-area QRS axes of the upper row were obtained by dividing the QRS loops planimetrically. Simultaneously recorded scalar leads were used for the timing of instantaneous vectors.[10,11] The mean half-area axis of the lower row (broken line) was obtained by averaging the time of incidence of the three planar half-area QRS axes in the upper row. The spatial angle between SÂQRS and the mean half-area QRS axis is 12° (only the direction of SÂQRS is indicated, not its magnitude).

Because of the elongated and peaked configuration of T loops, a maximal T vector (instantaneous T vector of largest magnitude) could be taken as representative for cardiac recovery without introducing a significant error. This obviated time-consuming graphic procedures for the determination of a representative spatial T vector. Maximal T vectors were found to be identical in all planes, without exception.[11]

The spatial QRS-T angle can be calculated using the following equations:

$$V_1 = \sqrt{X_1^2 + Y_1^2 + Z_1^2}$$

V_1 = spatial magnitude of QRS vector.

$$V_2 = \sqrt{X_2^2 + Y_2^2 + Z_2^2}$$

V_2 = spatial magnitude of T vector.

$$\cos \Theta = \frac{X_1 X_2 + Y_1 Y_2 + Z_1 Z_2}{V_1 V_2}$$

X_1, Y_1, Z_1 = scalar magnitudes of QRS vector
X_2, Y_2, Z_2 = scalar magnitudes of T vector
angle Θ = spatial QRS-T angle.

On the basis of the above equations, Helm[14] designed a table by which the spatial QRS-T angle can be read off to the nearest 5 degrees. By applying such trigonometric functions, it is possible to obtain the necessary spatial information using only two plane projections, since all spatial data are contained in two planes. In the present study the spatial QRS-T angle was determined from the frontal and horizontal planes.

RESULTS

When the method described above was applied, a mean spatial QRS-T angle of 56° ± 18.8° was found for the corrected orthogonal vectorcardiogram. The lowest and highest values obtained were 20° and 105°, respectively. The standard error was 2.5°. Helm's tables[14] were used throughout the study.

DISCUSSION

The clinical significance of spatial QRS-T relations has been widely stressed in the past by many electrocardiographers. For example, positive correlations with other clinical data such as cardiac work have been demonstrated.[6,7] The scarcity of quantitative studies in spite of numerous methodological reports[1,3,4,15] may be explained by shortcomings of the applied procedures, as follows:

1. In vector electrocardiography[1] spatial QRS-T angles are estimated from plane projections (frontal and horizontal). Such estimations may lead to large errors, as illustrated in Fig. 2. Furthermore, in the vast majority of cases, maximal QRS vectors were not found to be identical in all planes. A mean angular discrepancy of 34° ± 33.9° was found between the maximal QRS vectors of the frontal and horizontal planes.[11] Since by definition an angle has only two sides, such QRS vectors cannot be used for an analysis of spatial QRS-T angles.

2. So-called mean QRS vectors have also been obtained by plotting vectors from peak deflections of scalar leads.[15] Because of the time discrepancies between scalar peak deflections of different leads,[11] such vectors are also not identical in all planes. A mean angular discrepancy of 19° ± 14.9° (range 72°) was found between such vectors of the frontal and horizontal planes.[11]

3. The most accurate method to determine the true mean QRS vector is that described by Ashman and co-workers.[13] All parameters of QRS, namely, time and voltage, are taken into account. The method described in this study proved to be less time-consuming than Ashman's. It appears from the study of Simonson and co-workers[16] that the direction of SÂQRS is of greater significance than its magnitude. Therefore, the method described in this study may supplant the area integration of scalar leads, at least in vectorcardiography.

The pitfalls of planar vectorcardiography in common use today have not been stressed sufficiently. Such recordings do not lead necessarily to spatial evaluations of vectors unless these vectors are identified carefully in all planes. The discrepancies between different analytic methods illustrate the fallacies of this type of recording.[11,12] By the use of more reliable methods, quantitative studies should be facilitated and thereby provide a better discrimination between pathologically significant and insignificant T changes.

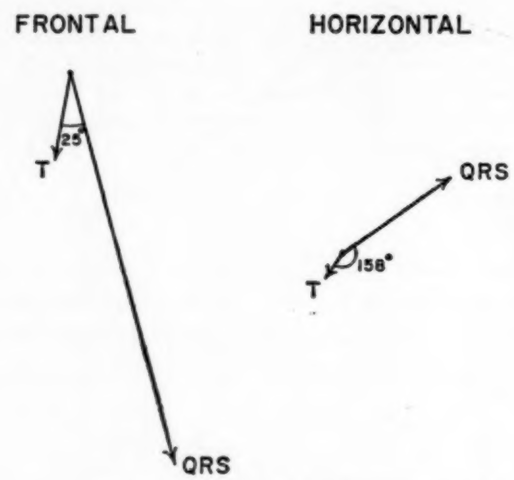

Fig. 2.—An illustrative example of the errors which are encountered when spatial QRS-T angles are estimated from plane projections. The spatial QRS-T angle in this case is only 37°. The large projected angle in the horizontal plane, however, may lead to an erroneous estimation of the spatial relationship between QRS and T.

SUMMARY

The spatial QRS-T angle was determined in a group of 50 normal subjects. A corrected orthogonal vectorcardiographic lead system was used. A new method for the determination of spatial angles from planar vectorcardiograms was designed. Its accuracy approached that for Ashman's SÂQRS. The normal spatial QRS-T angle was found to be 56° ± 18.8°. Errors of spatial analysis in some commonly used methods were discussed.

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Hypertension Due to Unilateral Renal Arterial Obstruction: Preliminary Observations on the Contribution of Differential Renal Clearance Studies

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That severe arterial hypertension can be caused by any lesion that impairs blood supply to one kidney is now well documented.[1-5] It can often be cured by restoration of normal blood flow or by removal of the affected kidney. We recently reported our experience with 8 such patients treated surgically at Ochsner Foundation Hospital.[6] Five underwent conservative surgical procedures which gave relief of symptoms in every case, with restoration of normotension in 3 patients for 1, 6, and 24 months, respectively, and considerable improvement in blood pressure in 2 for 6 months. Nephrectomy was performed in 3 patients, with complete relief of symptoms and hypertension in 2 of them for 5 years and 10 months, respectively, and with death from cerebral insufficiency in 1 within 5 weeks. In 2 others the renal arterial stenosis, as determined by measuring the pressure proximal and distal to the obstruction, proved insignificant.

The problem now is not validation of the concept of arterial hypertension as being secondary to renal arterial stenosis, or even selection of the correct surgical technique to be utilized. It is, rather, one, first, of selecting those patients with arterial hypertension in whom suspicion of unilateral renal arterial obstruction is sufficiently great to justify further study, and, secondly, of evaluating the information thus obtained.

The purpose of this paper, therefore, is to present our criteria for selecting such patients for further study, to compare the validity of the information obtained by aortography with that obtained by differential renal function studies, and to comment briefly on one facet of the information derived from differential renal function studies which seems pertinent to the concept of arterial hypertension in general.

Arterial hypertension is relatively common. Aortography, performed with use of a local anesthetic, by rapid injection of 20 ml. of a 50 per cent solution of Hypaque through a large bore No. 18 French needle, is both uncomfortable and, to some extent, hazardous. Performance of differential renal function studies,

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after introduction of a cystoscope and with temporarily indwelling No. 8 French ureteral catheters, is most uncomfortable for the patient. In addition, there is danger of introducing infection. For these reasons, neither procedure should be used routinely to evaluate arterial hypertension. On whom, then, and in what order are these procedures indicated?

SELECTION OF PATIENTS

History.—We have not been impressed with any characteristic features in the history of these patients. The hypertension is usually severe, with a high, fixed diastolic pressure and rapid progression of all clinical manifestations.[7] But this is not necessarily true. One of our patients, whose history was most bizarre, at no time had a recorded blood pressure in excess of 200 mm. Hg systolic and 100 mm. Hg diastolic, and yet, now, after endarterectomy, he is normotensive. Others[1] have been impressed with the appearance of polyuria and leukocytosis; yet, leukocytosis we have not detected, and polyuria and polydypsia were present in only one child. In our adult patients we have been impressed with an overwhelming inner tension and restlessness that was unexplainable to us and the patient.

Physical Examination.—The sole helpful physical finding has been an audible bruit over one or both femoral arteries. This is ancillary evidence only, but demonstration of atherosclerosis in one location makes its presence in another location more likely. We hold it to be sufficiently important to demand inclusion of palpation and auscultation of the femoral arteries (actually, all available arteries) in the routine examination of all patients with arterial hypertension.

Laboratory Procedures.—The usual laboratory procedures have proved of little help. Renal function, as crudely measured, if measured at all, by excretory urography, is normal, and only slight diminution in the size of the affected kidney may be discerned in excretory or retrograde pyelograms (Fig. 1). The usually employed renal function tests also invariably yield normal results and the urine sediment is bland.

At present we are forced to rely on our knowledge of the natural history of hypertension (and this knowledge can be had only after detailed questioning of many patients with arterial hypertension) and on the concept that arterial hypertension is overwhelmingly a disease of the third and fourth decades of life, rarely beginning in persons younger than 30 years or older than 50 years. We therefore select for further study patients: (1) whose hypertension began before the age of 30 years; (2) whose hypertension began after the age of 50 years, particularly, if it accelerates rapidly; (3) with fixed arterial hypertension and an audible bruit over one or both femoral arteries; (4) with unexplained difference in size or function of the two kidneys on excretory urography; (5) with a kidney which appears as nonfunctioning on excretory urography and as normal on retrograde urography; (6) whose hypertension suddenly gets more severe; and (7) whose history, for reasons that we cannot always verbalize, seems in some way at variance with what experience would lead us to expect. We apologize for the vagary of this concept, but in medicine it is at times necessary to "feel one's way" to a diagnosis that eludes conscious formulation.

Unfortunately, the accuracy of these criteria cannot as yet be assessed, since we do not know how many we might have found had we searched routinely. We believe that as time elapses our criteria will be broadened rather than made more rigid.

Aortography.—Carefully performed and interpreted aortography has proved most helpful. For reasons to be given later, we now prefer to postpone it until after differential renal function studies have been performed. When a definite lesion is demonstrable, aortography alone is sufficiently reliable to justify surgical exploration. We have had some difficulty in interpreting films in which stenosis is questionable, and have twice found, at operation, that accurate measurement of the arterial pressure proximal and distal to the stenosis revealed no significant lowering of pressure below the stenosis. In each instance we were forced to conclude that the stenosis was not a significant etiological factor in the hypertension, and so we did not tamper with it. That a more sensitive test to complement aortography would be helpful was soon apparent, and for that reason we turned to differential renal function tests.

TABLE I. COMPARISON OF VARIOUS ESSENTIAL RENAL FUNCTIONS DETERMINED BY DIFFERENTIAL RENAL CLEARANCE STUDIES

PATIENT	CORRECTION* FOR SURFACE AREA	KIDNEY	URINE (C.C./MIN.)	R.P.F. (C.C./MIN.)	G.F.R. (C.C./MIN.)	INULIN U/P	Tm_{PAH} (MG./MIN.)	URINE Na (mEq./L.)	% FILT. Na EXCR.	% FILT. H_2O EXCR.	SODIUM U/P
Patients With Hypertension and No Demonstrable Unilateral Renal Artery Obstruction											
I	0.87	Left	1.5	75.9	52.4	39.5	17.8	149	2.5	2.2	1.1
		Right	1.2	67.8	48.7	44.5	16.7	148	2.2	1.9	1.09
II	1.07	Left	4.39	281	80.4	23.3		29.3	0.9	6.3	0.21
		Right	4.13	269	74.8	25.0		29.9	0.9	6.4	0.21
Patients With Hypertension and Unilateral Renal Artery Obstruction											
III	0.98	Affected	0.41	186	43.6	129.7	33.0	18.0	0.1	1.1	0.13
		Contralateral	3.7	239	56.8	19.4	37.8	75.3	2.7	6.1	0.52
IV	1.01	Affected	0.52	61	23.4	44.1	16.4	37.7	0.6	2.3	0.28
		Contralateral	3.1	76.6	27.0	8.9	14.5	31.7	2.8	11.9	0.23
Patient With Hypertension Associated With Unilateral Atrophic Pyelonephritis											
V	1.04	Affected	1.5	88	21.4	14.0	11.3	102	5.8	8.8	0.71
		Contralateral	4.5	380	86.7	19.2	50.5	117	4.6	6.0	0.81

*All values except ratios corrected to 1.73 square meters of body surface.

USE AND INTERPRETATION OF DIFFERENTIAL RENAL FUNCTION TESTS

Method.—The following procedure was used on 5 patients. All received approximately 1,000 ml. of water in the hour preceding the test. This was supplemented with intravenous administration of 1 L. of a 5 per cent solution of dextrose in distilled water in one patient whose urinary flow was initially inadequate. Sodium Luminal (2 grains) intramuscularly, morphine sulfate (¼ grain) intramuscularly, or Nisentil (30 mg.) intravenously was then administered. After topical application of lidocaine hydrochloride or piperocaine hydrochloride, cystoscopy was performed by a member of the Department of Urology, and a No. 7 or, if the ureter would not accommodate this, a No. 6 "whistle-tip" ureteral catheter was introduced into each ureter. When urine

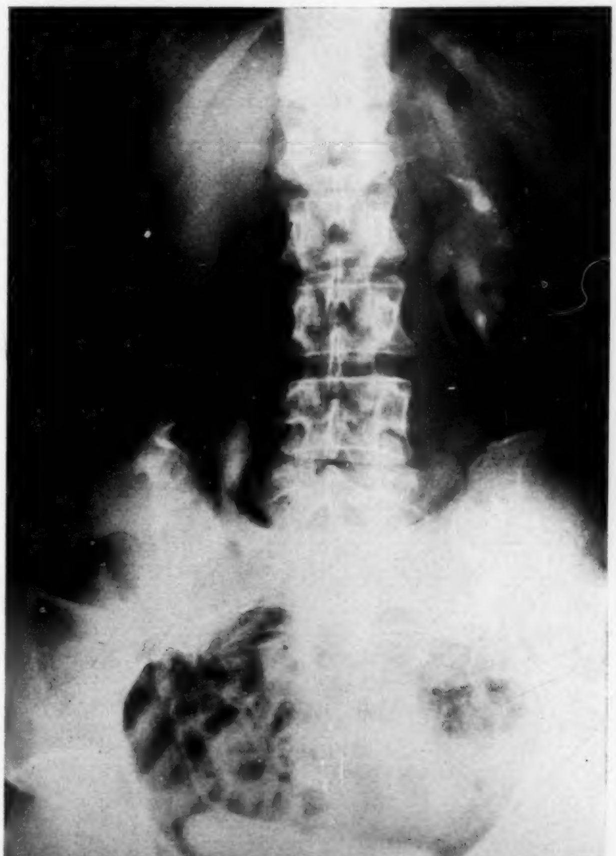


Fig. 1.—Excretory urogram of a patient with severe hypertension due to unilateral atrophic pyelonephritis on the left side (Case V).

was demonstrated to flow freely from each catheter, the cystoscope was removed and a Coudé No. 16 catheter was inserted into the bladder. The patient was then transferred to a comfortable bed. Urine was obtained from each catheter for determination of the inulin blank. A Lewisohn needle was next inserted into an antecubital vein to permit repeated withdrawal of blood without use of a tourniquet. A blood sample was collected for determination of the inulin and para-aminohippurate (PAH) blank. A priming infusion of para-aminohippurate and inuiln was then started, followed by a sustaining infusion calculated to maintain a plasma level of 15 to 20 mg. per

cent of inulin and 2 to 3 mg. per cent of para-aminohippurate. Forty-five minutes was allowed for equilibration and the test was begun. The by now standard "clearance procedure," as outlined previously,[8] was used, with the exception that urine was collected separately from each ureter and from the bladder. All chemical analyses were done in duplicate by the methods previously described, with the exception that the concentration of sodium was determined with the aid of a flame photometer. An antibiotic was routinely administered for 3 days after the test as prophylaxis against infection.

A complete table and set of graphs was made for each patient. To facilitate presentation, we are including a composite table of the most important measurements made on all patients (Table I) and bar graphs, in order to compare the actual difference of the behavior of the two kidneys as well as this difference expressed in per cent (Fig. 2). All calculations were made as previously outlined. Since it will be discussed later in detail, the percentage of filtered sodium excreted (tubular rejectate fraction of sodium) was calculated as:

$$\frac{\text{clearance of sodium}}{\text{clearance of inulin}} \times 100$$

or, more simply, as:

$$\frac{U_{Na}/P_{Na}}{U_{in}/P_{in}} \times 100$$

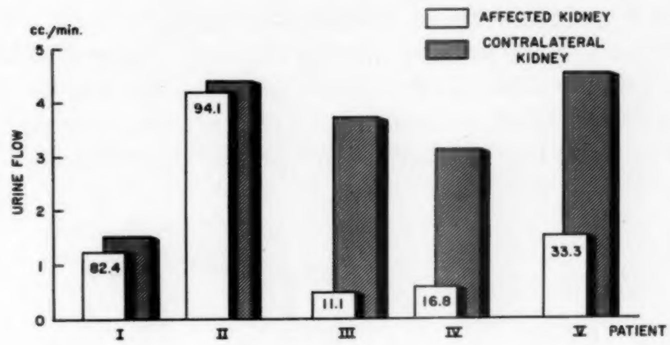
RESULTS

The results can be best described by grouping the patients according to their conditions.

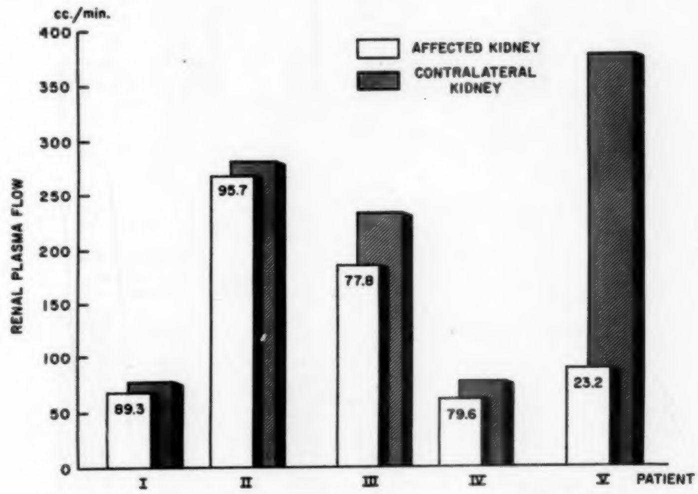
A. *Patients Whose Renal Function Was Equal on Both Sides.—*

Patient I, a 68-year-old man, had had severe hypertension (at one time recorded as 240/190 mm. Hg) of 2 years' duration and two episodes of transient cerebral vascular insufficiency. There was no aortographic evidence of renal arterial obstruction, but the likelihood of such obstruction prompted us to pursue our studies further with a differential "clearance." No significant difference was found in the function of the two kidneys. Noteworthy is the general bilateral depression of renal function associated with the extremely high filtration fractions of 0.75 and 0.71. This would indicate intense efferent arteriolar constriction with an extremely high intraglomerular pressure. We now attribute it to the introduction of Hypaque into the aorta 3 days previously (Table II). This suggests that if a differential clearance is to be done, it should be done prior to aortography. It is highly probable that operation should not be performed for several days after aortography, or until all evidence of renal vasoconstriction has disappeared.

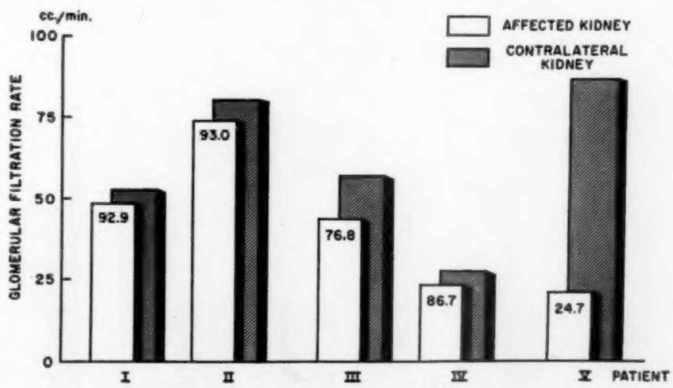
Patient II, a 36-year-old man, had had known mild hypertension for the preceding 10 years. He possessed all the characteristics of pseudoxanthoma elasticum. In addition to the classical changes in his skin and fundi, calcified femoral arteries could be demonstrated roentgenographically, and a bruit was present in each femoral artery. Disease of one or both renal arteries was suspected, and, as will be discussed later, the extremely low tubular rejectate fraction of sodium and water bilaterally (0.9, 0.9 and 6.3, 6.4, respectively) (Fig. 2, *F* and *I*; Table I) suggests that this is indeed the case. We do not believe that operation is justified at the present time.



A.



B.



C.

Fig. 2.—Comparison of various essential renal function studies in the affected and contralateral kidneys. Patients I and II had no demonstrable unilateral renal arterial disease. Patients III and IV each had stenosis of one renal artery. Patient V had severe unilateral atrophic pyelonephritis. Figures on the ordinate are absolute values. Figures inside the bars are percentage variations in function of the affected kidney, considering the contralateral kidney as 100 per cent.

B. *Patients With Proved Renal Arterial Obstruction.*—

Patients III and IV demonstrated greatly reduced urinary flow, renal plasma flow, glomerular filtration rate, and tubular rejectate fraction for sodium and water on the affected side (0.1 per cent and 0.6 per cent, respectively, for sodium) (Fig. 2, *A-C*, *F*, *I*; Table I). Inversely, the U/P-inulin ratio was comparatively

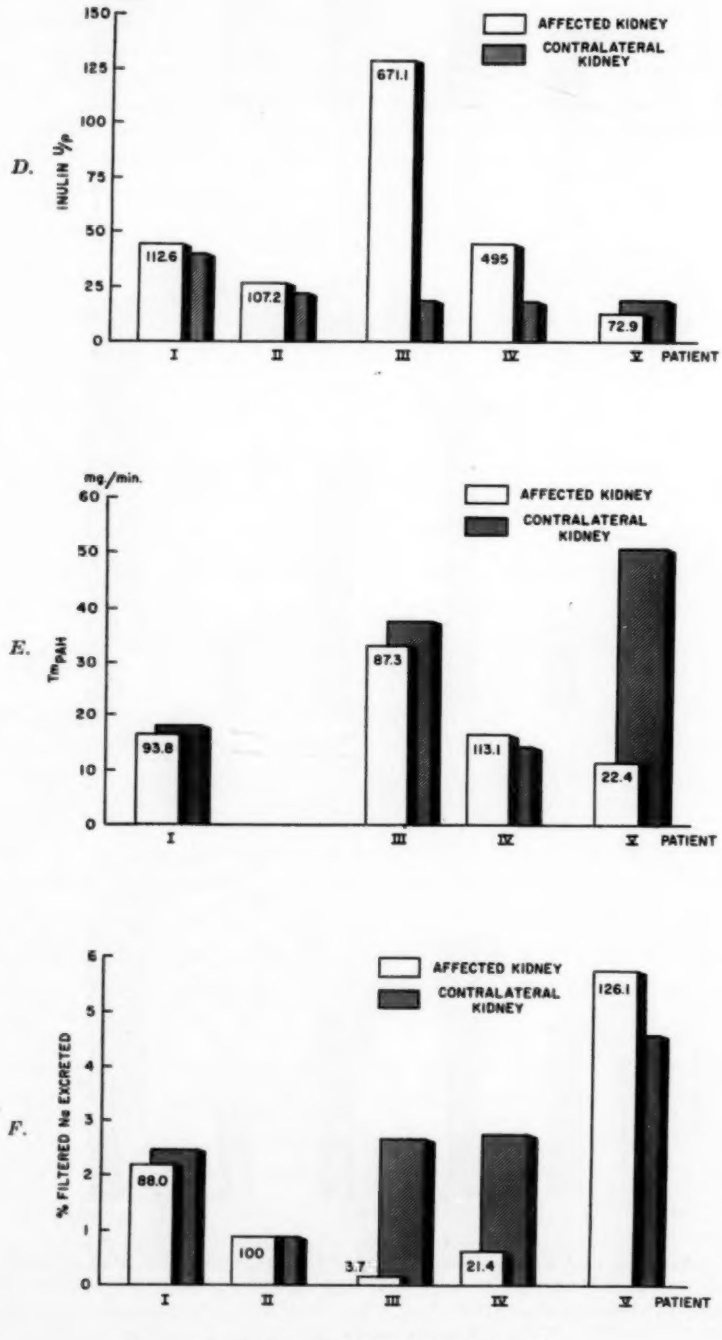
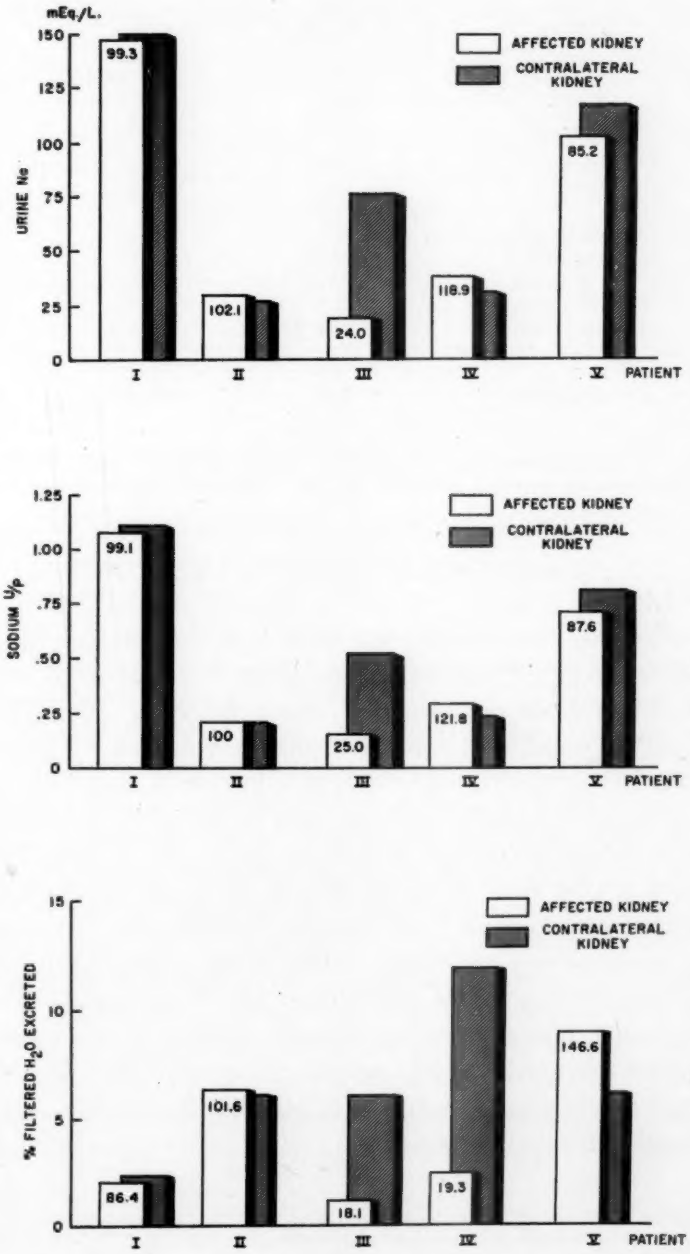


Fig. 2.—*D, E, F.* (*For legend see page 621.*)

higher on the affected side (129.7 and 44.1, respectively). The concentration of sodium in the urine and the U/P ratio of sodium were both lower on the affected side, in comparison with the unaffected side, in Patient III but slightly higher in Patient IV (Fig. 2, *G*, *H*; Table I). Note that in Patient III aortography had been performed 3 days before the clearance studies and, again, his kidney showed general reduction in function. This demands cautious interpretation of the data,



G.

H.

I.

Fig. 2.—*G, H, I.* *(For legend see page 621.)*

since we cannot be certain that one kidney did not receive a disproportionate amount of Hypaque. Yet, the values are such that comparison of the function of the kidneys seems valid even though the function of each kidney was proportionately or even disproportionately reduced.

TABLE II. THE EFFECT OF DIODRAST INJECTION ON VARIOUS RENAL FUNCTIONS*

PATIENT	KIDNEY	R.P.F. (C.C./MIN.)	G.F.R. (C.C./MIN.)	FILTRATION FRACTION
I	Right Left	67.8 75.9	48.7 52.4	0.75 0.71
II	Right Left	269 281	74.8 80.4	0.28 0.29
III	Affected Contralateral	186 239	43.6 56.8	0.23 0.24
IV	Affected Contralateral	61.0 76.6	23.4 27.1	0.38 0.36
V	Affected Contralateral	88 380	21.4 86.7	0.24 0.23

*In Patients I and IV the clearance study was carried out shortly after aortography (within 3 days) In Patients II and V aortography followed clearance studies. The aortogram was done several months before clearance studies in Patient III.

C. *Patient With Hypertension Associated With Unilateral Atrophic Pyelonephritis.*—

Patient V, a 54-year-old woman, has been included because her case illustrates yet another value of a "differential clearance." Severe hypertension and left pyelonephritis had been discovered 4 years prior to admission. Renal function was grossly normal, and the intravenous pyelogram (Fig. 1) revealed blunted calyces on the left, with slight decrease in size of that kidney. Differential clearances, however, showed greatly reduced function of the left kidney, with a high tubular rejectate fraction of sodium and water by both kidneys, and a correspondingly low U/P ratio of inulin (Fig. 2, *D*; Table I). Following these tests, a severe attack of recurrent pyelonephritis developed; after this was controlled, left nephrectomy was performed. The blood pressure fell immediately from an average hospital control of 190/110 to 140/80 mm. Hg. This patient has been observed only 2 weeks postoperatively, so that it cannot yet be concluded whether the hypertension is less severe. It is significant that the urinary sodium concentration was higher on the affected side (Fig. 2, *G*). There was no demonstrable bleeding from either ureter.

DISCUSSION

Patients I and II appear to indicate that a differential clearance can adequately demonstrate absence of unilateral renal disease, and may render aortog-

raphy unnecessary. Patients I and IV also serve to indicate the degree to which aortography produces intensive efferent arteriolar spasm and depresses renal function in general for at least 3 days.

Patients III and IV, each with surgically proved and corrected obstruction to one renal artery, indicate the ease with which renal arterial obstruction can be delineated.* Table III shows a comparison of the results of clearance studies on the kidney with unobstructed blood flow (considered as the "hypertensive" kidney) and the affected kidney (considered as the "hypotensive" kidney).

TABLE III. COMPARATIVE DATA OBTAINED FROM THE "HYPERTENSIVE" AND "HYPOTENSIVE" KIDNEYS

FUNCTION MEASURED	"HYPERTENSIVE" KIDNEY	"HYPOTENSIVE" KIDNEY
Urine Flow	Normal to increased	Decreased
Renal Plasma Flow	Normal to increased	Decreased
Glomerular Filtration Rate	Normal to increased	Decreased
Tm_{PAH}	Normal to increased	Decreased
Tubular Rejectate Fraction of Sodium	Increased	Decreased
Tubular Rejectate Fraction of Water	Increased	Decreased
U/P Sodium	Variable	Variable
Urine Sodium Concentration	Normal to increased	Usually decreased
U/P Inulin	Decreased	Increased

Urine Flow.—Consideration of Fig. 2,*A* and Table I would suggest that perhaps the most constant finding is a low volume of urine from the affected, or hypotensive, kidney (Conner and associates[9] require a 60 per cent reduction). Although this is true, the vagaries of ureteral irritation and spasm are such that we hesitate to rely on this alone. It might be reliable if it were supplemented with a simultaneous recording of renal intrapelvic pressure to indicate false depression of urine flow secondary to ureteral spasm or thrombotic obstruction.

R.P.F.—G.F.R.—Tm_{PAH}.—Renal plasma flow and glomerular filtration rate (Fig. 2, *B*, *C*; Table I) were invariably decreased, but this is of necessity nonspecific, since any unilateral renal disease might be expected to result in a decrease in blood flow or filtration rate. The decreased Tm_{PAH} (Fig. 2, *E*; Table I) is evidently of even less diagnostic value and, since to measure it prolongs the patient's discomfort by 45 minutes, we have discontinued this determination.

Tubular Rejectate Fraction of Sodium and Water, U/P-Sodium Ratio, and Urinary Concentration of Sodium.—Several years ago it was demonstrated that in hypertensive subjects the tubular rejectate fraction of sodium and water, under conditions of a salt load, is significantly greater than in normal subjects.[8] Examination of the data in Patients III and IV appears to offer evidence that this is indeed true even in the absence of a salt load. In each instance the hyper-

*At the time of operation the arterial pressure was measured in the aorta and distal to the obstruction in the renal artery by means of a Sanborn electromanometer and a two-channel Sanborn Poly-Viso recording apparatus. The actual measurements were as follows: Case III—aorta, 160/110 mm. Hg; distal to obstruction, 120/100 mm. Hg. Case IV—aorta, 140/100 mm. Hg; distal to obstruction, 60 mm. Hg with little pulsation.

tensive kidney rejected a comparatively higher percentage of filtered sodium, 2.7 and 2.8 per cent, respectively (average normal 1.4 per cent with a range of 1.3 to 1.5 per cent), while the opposite kidney, protected as it was from the ravages of hypertension by the obstruction, and being actually by measurement a hypotensive kidney with a small pulse pressure, rejected but 0.1 and 0.6 per cent of sodium, respectively (Fig. 2, *F*; Table I). This relationship can evidently be demonstrated only when one determines the comparative sodium rejectate fraction of the hypertensive and the hypotensive kidney simultaneously. Otherwise, a salt load appears to be a necessary adjuvant. This is further confirmed by the high sodium tubular rejectate fraction of the pyelonephritic kidney (Patient V— Fig. 2, *F*; Table I) which, atrophic and possibly responsible for the hypertension, was not protected from the ravages of the latter.

As a further corollary to this, by examination of Fig. 2,*I* and Table I it can be seen that the tubular rejectate fraction of water is likewise increased in the hypertensive kidney and decreased in the hypotensive kidney. The final concentrations of sodium in the urine, suggested as a definite diagnostic test by Conner and associates[9] if it is 15 per cent lower on the affected side, is therefore influenced to a considerable extent by whether more or less water or more or less salt is rejected by the tubules, and this, in turn, may explain why we found a slightly higher concentration of sodium in the urine of the affected kidney in Patient IV and only a 12 per cent reduction in Patient V. This suggests that, basically, measurement of the tubular rejectate fraction of sodium and water is of more value than reliance on the urine sodium concentration, which is a final reflection of two variables.

We do not know why the hypertensive kidney rejects a disproportionate amount of sodium and water, and why the hypotensive renal tubules avidly reabsorb sodium and water. It is tempting to think it is simply some function of pressure itself, but it is clear that a decrease in renal plasma flow a priori could also mean a decrease in the delivery of a hormone or hormones that affect the tubular reabsorption of salt and water. The source of the hormones, if they exist, is obscure and their identity is unknown. As suggested indirectly by Berliner and Davidson,[10] it is equally plausible to assume that in the hypotensive kidney the increased reabsorption of sodium and water is related to a decreased tubular load. Conversely, the tubules of the hypertensive kidney, because of an increased intraglomerular pressure, would be presented with a relatively larger load of sodium and water and, therefore, would reject a relatively larger percentage. Whether the primary mechanism is an increase in rejection of salt or of water must remain moot until more data are available. We only know from past experience and from the results herein presented that this is the fashion in which hypertensive kidneys behave, and we can therefore employ it as a diagnostic tool.

U/P-Inulin.—The U/P-inulin ratio can be seen to be invariably above 1 and always comparatively higher in the urine from the hypotensive kidney (Fig. 2, *D*; Table I); this reflects the insatiate thirst of the hypotensive kidney for salt and water, and may have a practical application. It would be greatly to the patient's advantage if a simple test could be employed which would serve as

a check upon the validity of comparative urine flows and yet not be so time consuming or uncomfortable as the procedure for a full inulin-PAH clearance, with determination of at least sodium in addition. For reasons already given, we do not believe that the sodium concentration in the urine from the affected kidney is of necessity always low, even though it may usually be so. The U/P ratio of inulin would logically serve as just such a check upon the validity of the urine flow, and would have the additional advantage, being a ratio, in that it would be unaffected by leakage around the catheter and would demand only that a sufficient quantity of urine be obtained from each catheter to make the chemical determination after the period of inulin-PAH equilibration had been completed. That this may be reliable is suggested by determinations made in one patient whose aortogram indicated obstruction in the left renal artery but whose "clearance" was discarded because of excessive leakage from one ureteral catheter. The inulin-U/P ratio was 56.8 from the surgically proved unaffected kidney and 77.3 from the affected kidney. Furthermore, a change in the U/P-inulin ratio would presumably be reflected by a similar change in the U/P ratio of urea or creatinine, and this could easily be determined in one or two 15-minute clearance periods, at a considerable reduction in discomfort to the patient. This would be true, of course, only in patients with obstruction of one renal artery. It is still a theoretic derivation and requires absolute proof before one can rely entirely on the two simple determinations of urine flow and U/P ratio of either urea or creatinine.

Conner and associates[9] stressed the importance of care in performing and interpreting differential urinary studies, and we heartily confirm this. In our experience, leakage around a ureteral catheter and bleeding tend to occur together, and an attempt to extrapolate back to what would have been true if no leakage or bleeding had occurred is risky. Rather than do that we have discarded two clearances and relied entirely on aortography.

Two major pieces of information are lacking. A larger series would be desirable, but we have not found renal arterial obstruction to be a common lesion and we cannot foretell when the next valid suspect will present himself. Glaring is the fact that not once can we report the result of a comparative postoperative "clearance." Our scientific interest is equal to the task but the zeal of our patients is small, once they have survived the surgical procedure, been "cured" of their hypertension, and so have little to gain from the procedure; all have so far denied our request.

SUMMARY AND CONCLUSIONS

1. Severe arterial hypertension can be caused by any lesion that impairs blood supply to one kidney.

2. This lesion can best be demonstrated by the combination of a differential renal clearance test and aortography. Since both are uncomfortable for the patient and potentially hazardous, we select for further study patients: (a) whose hypertension began before the age of 30 years; (b) whose hypertension began after the age of 50 years; (c) with fixed arterial hypertension and an audible

bruit over one or both femoral arteries; (d) with unexplained difference in size or function of the two kidneys on excretory urography; (e) with a kidney which appears as nonfunctioning on excretory urography and as normal on retrograde urography; (f) whose hypertension suddenly gets more severe; and (g) whose history, for reasons that we cannot always verbalize, seems in some way at variance with what experience would lead us to expect.

3. Aortography alone is reliable when a definite lesion is demonstrable. It alone is not reliable when questionable stenosis is demonstrated.

4. Aortography is capable of producing severe renal arteriolar spasm with over-all depression of renal function and a high filtration fraction. These findings may persist for as long as 3 days. Therefore, differential renal clearance studies should be performed before aortography, and operation should be postponed at least 3 days after aortography.

5. Differential renal clearance studies are capable of clearly delineating the presence or absence of unilateral renal arterial obstruction.

6. In the presence of unilateral renal arterial obstruction there is an over-all reduction of renal function on the involved side, with a decreased tubular rejectate fraction for sodium and water, a variable concentration of sodium in the urine and a variable U/P-sodium ratio, and an increased U/P ratio of inulin. Conversely, the unobstructed or "hypertensive" kidney shows increased tubular rejectate fraction for sodium and water and decreased inulin-U/P ratio.

7. It is suggested that the combination of a decreased urine flow and an increased U/P-inulin ratio on one side may prove to be diagnostic of unilateral renal arterial obstruction.

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Refractory Edema Treated With Calcium Chloride in Combination With Mercurial Diuretics

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INTRODUCTION

Edema is common in congestive heart failure and cirrhosis of the liver. Most patients may be maintained edema-free by conservative measures such as bed rest, salt restriction, mercurial diuretics, and digitalis when indicated. At some time in the natural history of these diseases, however, edema may prove resistant to such therapy. Under such circumstances the production of a hyperchloremic acidosis with the use of oral ammonium chloride alone or in combination with acetazoleamide (Diamox) has been successful in re-establishing responsiveness to mercurial diuretics.[1]

In recent years the potential dangers of ammonium compounds in patients with liver dysfunction have been recognized. Clinical phenomena identical with those seen in hepatic coma, including mental disturbances, flapping tremors, neurologic signs, electroencephalographic changes, and elevated blood ammonia levels, have been described after the administration of ammonium-containing compounds.[2-4] For this reason, the use of the regimen of controlled hyperchloremia described above has been limited to patients with congestive heart failure. Altered liver function may be present in patients with congestive heart failure,[5] and even in this setting, ammonium intoxication has been described.[6]

Calcium chloride has none of these undesirable properties of ammonium chloride. After oral administration, chloride ion is absorbed from the gastrointestinal tract to a large degree, and hyperchloremia may be expected.[7] Until more effective agents were developed, calcium chloride was employed as a diuretic,[8,9] but it has not been popular since about 1930. However, its properties make it a useful substitute for ammonium chloride in producing hyperchloremic acidosis if liver dysfunction is present.

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TABLE I. COMPARISON OF BODY WEIGHT, PLASMA AND URINARY ELECTROLYTE CONCENTRATIONS IN PATIENTS ON TYPICAL REFRACTORY AND RESPONSIVE DAYS*

Diagnosis	LAENNEC'S CIRRHOSIS								CONGESTIVE HEART FAILURE				
Patient	L.W.	W.N.[1]	W.N.[2]	A.S.	M.B.	J.V.	T.M.	J.G.	S.S.	C.G.	W.N.	W.J.	T.J.
Refractory Day													
Plasma													
Na (mEq./L.)	136	138	138	129	136	131	143	130	138	132	134	129	133
K (mEq./L.)	3.1	4.2	4.3	3.5	3.1	4.3	5.0	4.2	4.0	3.7	4.1	4.6	3.5
Cl (mEq./L.)	105	107	113	109	106	104	102	115	112	101	102	—	97
CO_2 (mM./L.)	28.4	23.3	27.5	25.2	24.2	25.0	38.0	27.0	27.6	28.3	19.8	30.0	31.7
pH	7.44	7.42	7.39	7.49	7.45	7.38	—	—	7.37	7.40	7.30	—	7.36
Urine													
Vol. (c.c./24 hr.)	950	850	900	350	900	1,000	800	1,900	1,100	200	1,000	850	950
Na (mEq./L.)	35	—	39	9	9	24	—	—	65	—	—	—	40
Cl (mEq./L.)	52	—	84	26	7	5	—	13	83	—	0.6	—	81
Weight Change (Kg.)	+0.8	+0.8	+0.7	+2.0	0	+0.5	+0.5	+0.9	−0.3	+0.8	+0.5	+1.0	+0.5
Responsive Day													
Plasma													
Na (mEq./L.)	136	137	141	133	137	133	130	135	132	137	133	128	128
K (mEq./L.)	3.7	4.2	4.1	3.5	3.4	4.1	3.9	4.0	4.2	5.0	5.8	4.9	4.1
Cl (mEq/L.)	118	130	124	124	126	114	123	117	122	118	102	115	129
CO_2 (mM./L.)	15.8	16.2	18.0	15.3	12.1	18.8	31.6	14.4	14.5	10.8	17.5	15.8	21.1
pH	7.35	7.28	7.36	7.33	7.29	7.33	7.28	7.33	7.19	—	7.15	7.29	7.27
Urine													
Vol. (c.c./24 hr.)	3,860	5,925	5,700	3,000	4,600	2,625	1,600	4,500	4,700	3,400	2,500	3,950+	5,300
Na (mEq./L.)	100	98	115	100	45	98	—	—	86	113	—	89	84
Cl (mEq./L.)	168	170	175	171	154	175	164	—	150	158	110	132	127
Weight Change (Kg.)	−4.2	−5.1	−3.6	−3.2	−4.5	−2.3	−2.3	−3.6	−4.3	−3.6	−2.1	−4.9	−4.1

*In each instance, 2.0 c.c. of Mercuhydrin was administered.

This report summarizes our experience in the treatment of 12 patients with refractory edema due to heart disease or cirrhosis of the liver. In each, creation of hyperchloremic acidosis through administration of oral calcium chloride solution alone or in combination with acetazoleamide re-established responsiveness to a mercurial diuretic. This experience is representative of similar treatment in over 50 patients in the past 3 years.

METHODS

Twelve patients during 13 hospital courses of therapy were chosen for study. Seven had Laennec's cirrhosis with marked liver dysfunction. Several were icteric, but none had evidence of esophageal varices. Five patients had congestive heart failure. Of these, 2 had laboratory evidence of marked liver dysfunction. All of the patients were on a stable regimen consisting of bed rest, salt-restricted diet, and maintenance dosage of digitalis if this medication was indicated. No complicating disease was present.

In each patient, body weight and measurement of urinary volume were recorded daily. During the entire period of observation, fluid intake was restricted to less than 1,500 c.c. a day. Frequent determinations of blood pH, plasma sodium, chloride, carbon-dioxide combining power, potassium, and urinary electrolytes were made. Levels of serum calcium were followed in selected patients. The laboratory methods for these determinations have been described previously.[1]

RESULTS

The administration of a mercurial diuretic in the setting of hyperchloremic acidosis produced a diuresis in every patient. Table I presents data from the 13 courses of treatment. The data are divided into 2 groups: (a) refractory period and (b) responsive period (responsiveness having been restored by the technique described). It should be noted that during refractory periods, plasma electrolyte concentrations were within normal limits. Injections of a mercurial diuretic produced no significant loss of weight or diuresis. During the responsive period when hyperchloremic acidosis was present, injection of a mercurial diuretic resulted in a marked diuresis in each patient. Blood pH and plasma carbon-dioxide combining power and chloride tended to return to normal levels, and as this occurred, decreased responsiveness to mercurials was observed even though edema persisted. When calcium chloride was administered to replace the chloride lost in the urine during diuresis, a sustained response to mercurial diuretics could be achieved.

The following case reports of 2 patients during 3 courses of therapy are presented in detail.

CASE 1.—C. G., a 68-year-old woman with chronic constrictive pericarditis, had had fluid retention for 15 years. During this period, digitalis had been administered daily. Pericardiectomy had been attempted unsuccessfully. The patient had been admitted to The New York Hospital 5 times for control of edema. On each occasion she had a good response to bed rest, salt restriction, and mercurial diuretics.

Her last admission, in 1954, was again prompted by gradual reaccumulation of edema and, on this occasion, ascites, despite the administration of mercurial diuretics biweekly. Physical examination confirmed the presence of marked peripheral edema and ascites. In addition, distended neck veins were noted. The liver was percussed 5 cm. below the right costal margin. Venous pressure was elevated clinically. Paradoxical pulse was present. Laboratory investigation revealed normal urinalysis, complete blood count, and plasma electrolyte concentrations.

Serum albumin was 2.3 Gm. per cent and globulin 1.7 Gm. per cent. Alkaline phosphatase was 6.8 Bodansky units. The Bromsulphalein test showed 15 per cent retention in 45 minutes.

The patient was placed on a regimen of bed rest, salt-restricted diet, and maintenance digitalis. On the second hospital day, 500 mg. of acetazoleamide and 8.0 Gm. of ammonium chloride were administered in an attempt to induce hyperchloremic acidosis. The patient became lethargic and mentally obtunded later in the day. Bilateral extensor plantar responses were noted. With discontinuation of ammonium chloride and acetazoleamide, abnormal signs disappeared. Subsequently, the administration of acetazoleamide alone, followed by mercurial diuretics, produced no signs of toxicity and a loss in weight of only 1 kilogram. Urinary volumes were less than 1,300 c.c. daily.

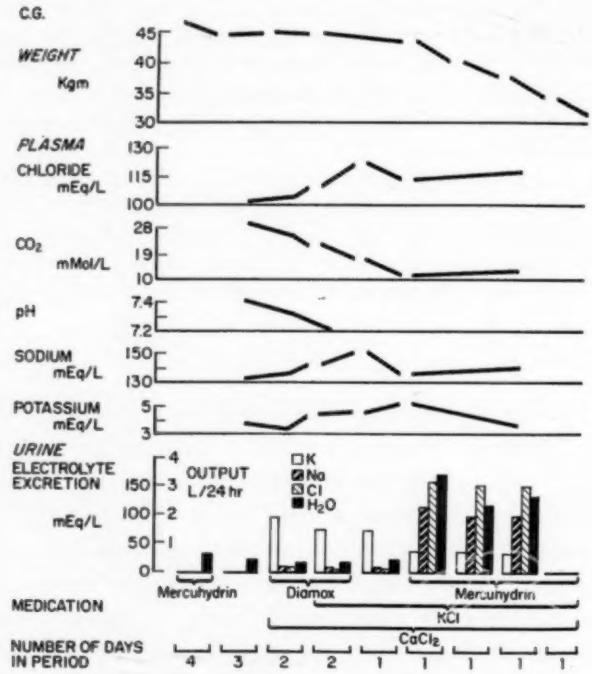

Fig. 1.—Case 1. This figure illustrates the course of Patient C. G. On the ordinate are listed the body weight; plasma sodium, potassium, chloride, carbon-dioxide combining power, and pH; urine sodium, potassium, and chloride concentrations; and total urinary volumes for 24-hour periods. On the abscissa are listed the medications and the number of days each was administered. The observation period is continuous. The bars represent the average daily urinary concentration of sodium, potassium, and chloride during the individual treatment periods.

The next 17 days of the patient's course are presented graphically in Fig. 1. During this time, hyperchloremic acidosis was achieved through the use of 15 Gm. of calcium chloride and 750 mg. of acetazoleamide daily. Blood pH fell from 7.40 to 7.20, carbon-dioxide combining power from 28.3 to 10.8 mM./L., and plasma chloride rose from 101 mEq./L. to a peak of 126 mEq./L. Supplementary potassium chloride was administered because of a plasma level of 3.3 mEq./L., in anticipation of further decrease during diuresis. After 4 days, acetazoleamide was discontinued, and after an additional 24 hours, mercurial diuretics were begun. With the first injection the patient had a marked diuresis and lost 3.6 kilograms. During continuing therapy over the next 4 days the patient lost 11.3 kilograms and showed a marked reduction in edema and ascites. Plasma electrolytes tended to return toward normal. The patient's mental status remained good.

Comment.—This patient had evidence of ammonium intoxication during the administration of ammonium chloride and acetazoleamide. Acetazoleamide alone

and in conjunction with calcium chloride produced no untoward effect. Although reports of hepatic coma after administration of acetazoleamide in patients with liver disease have appeared in the literature,[10] we have not observed this complication. Hyperchloremic acidosis was achieved with the administration of calcium chloride, and responsiveness to mercurial diuretics re-established with an excellent result.

Case 2.—W. N., a 62-year-old white man with Laennec's cirrhosis, was admitted to Bellevue Hospital because of progressive swelllng of the legs and the abdomen for 1 month. Physical examination revealed ascites and anasarca. Icterus was not present clinically. Laboratory investigation revealed a normal urinalysis. Hematocrit was 36 per cent. Cephalin flocculation was 4+ in 48 hours. Serum albumin was 3.8 Gm. per cent and globulin 1.0 Gm. per cent. Alkaline phosphatase was 4.4 Bodansky units, and the icteric index was 18. Total cholesterol and ester fraction values were 161 and 63 mg. per cent, respectively. Retention of Bromsulphalein was 80 per cent in 45 minutes.

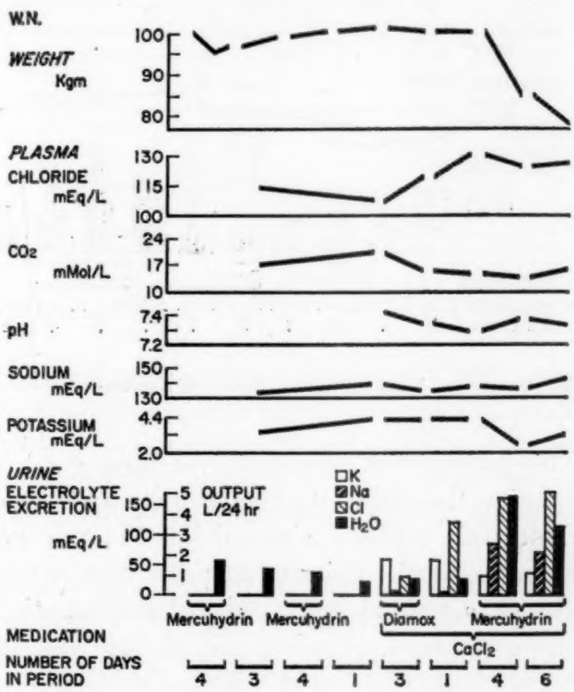

Fig. 2.—Case 2. Course 1. This represents the course of observation for W. N.

The patient's course is summarized in Fig. 2. He was placed on a regimen consisting of bed rest and a salt-restricted diet high in carbohydrate content. Initially, an injection of a mercurial diuretic produced a diuresis of 3,200 c.c. in 24 hours, with a loss in weight of 3 kilograms. Subsequently, 7 mercurial injections failed to produce a loss in weight. The patient was then placed on 10 Gm. of calcium chloride and 750 mg. of acetazoleamide per day for 3 days. Blood pH fell from 7.42 to 7.28, carbon-dioxide combining power from 23.3 to 16.2 mM./L., and plasma chloride rose from 107 to 130 mEq./L. Urinary chlorides rose from 8 to 124 mEq./L. One day after cessation of acetazoleamide therapy, mercurials were administered daily for 10 days, with a loss in weight of 21 kilograms, daily urinary volumes ranging from 2,200 to 5,925 c.c., loss of edema, and marked reduction in ascites. Plasma electrolytes tended to return to normal, although supplementary potassium chloride was necessary because of hypopotassemia during diuresis.

Course 2.—Over the next 11 days the patient regained 6.4 kilograms of weight, despite 3 mercurial injections. Calcium chloride and acetazoleamide were readministered in the same doses for 3 days. One day after cessation of acetazoleamide, mercurial diuretics again produced a significant diuresis, with a loss in weight of 7.7 kilograms in 6 days (Fig. 3).

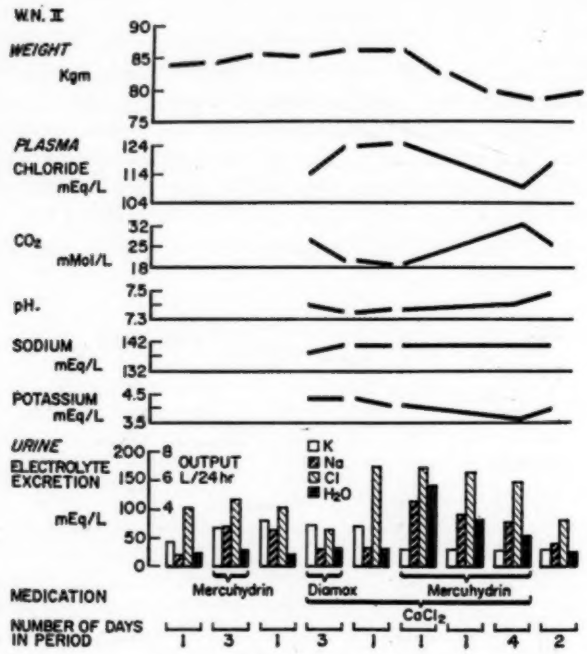

Fig. 3.—Case 2. Course 2. This represents the second course of observation for W. N.

Comment.—This patient with advanced liver disease had an excellent diuresis on two occasions during the administration of mercurial diuretics after the production of hyperchloremic acidosis with calcium chloride and acetazoleamide. No untoward effect was noted. Prior mercurial administration at a time when plasma electrolytes were normal had produced no diuretic response.

DISCUSSION

In these patients, calcium chloride has proved to be an effective, safe substitute for ammonium chloride in the production of hyperchloremic acidosis. In a previous communication[1] the theoretical advantages of a hyperchloremic state prior to the administration of mercurial diuretics had been discussed in detail. Several practical considerations may need re-emphasis.

Hyperchloremia and acidosis are achieved more readily when acetazoleamide is administered concomitantly with the source of chloride. Five hundred to 750 mg. per day in 1 dose has been effective. Calcium chloride is administered as 10 c.c. of a 25 per cent solution 4 times a day (10.0 Gm.). This compound has an unpleasant taste; it is a gastric irritant and produces gastric symptoms in

some patients. Postprandial administration in fruit juice may eliminate these objections. As illustrated by the case of J. G., hyperchloremia may be achieved with the use of calcium chloride alone.

During the course of acetazoleamide and calcium chloride, plasma pH or carbon-dioxide combining power and urinary chloride concentration should be determined daily. The former will provide a guide to the degree of acidosis, and the latter to the amount of chloride presented to the renal tubules. When the urinary chloride concentration rises sharply, usually to 40 mEq./L. or more under conditions of restriction of fluid to less than 1,500 c.c. a day, response to mercurial diuretics may be expected. Acetazoleamide should be discontinued for 24 hours prior to the administration of a mercurial, because of the antagonistic action of the two drugs on chloruresis.

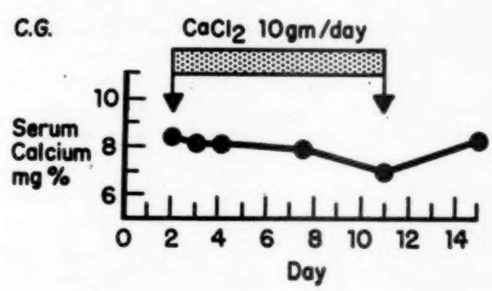

Fig. 4.—Serum calcium levels in Case 1., C. G., during the period of administration of calcium chloride.

In cases studied here and by other observers[7,11] little change in serum calcium levels during the administration of calcium chloride has been noted. The emergence of digitalis toxicity in digitalized patients has not been observed. Fig. 4 shows the serum calcium levels in Case 1. Note the low value of serum calcium initially and the slight decrease despite daily administration of calcium chloride.

Moderate degrees of acidosis are tolerated by these patients. The danger of extending the regimen to the point of symptomatic acidosis, however, is a real one. This has not been observed when proper laboratory controls have been employed. Frequent clinical and laboratory observations are essential.

SUMMARY

Data are presented on 12 patients with edema refractory to mercurial diuretics. During 13 periods of hyperchloremic acidosis induced by calcium chloride alone or in combination with acetazoleamide, responsiveness to mercurial diuretics was restored.

Calcium chloride has proved to be a safe, effective substitute for ammonium chloride as a source of chloride in this regimen. It may be employed in patients with liver disease.

Dr. R. Dexter, Dr. G. Frimpter, and Dr. N. Spritz contributed to the study of many of the patients. We are indebted to Mrs. Ruth Aronson, Miss Carolyn Register, and Miss Naomi

Schechter for their technical assistance. Diamox for this study was generously supplied by Dr. J. Gallagher, Lederle Laboratories.

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Book Reviews

Operable Herzleiden Einfuhrung in Klinic, Diagnostik und Operations-Moglichkeiten. By Prof. Dr. J. Jacobi and Prof. Dr. M. Loeweneck, Stuttgart, Georg Thieme Verlag.

This small book of 175 pages and 155 figures is a good concise survey of the present status of the ever expanding surgical field of repair of congenital and acquired angiocardiopathies. The text is profusely illustrated with, for the most part, clearly delineated illustrations, many of which are simple schematic line drawings, outlined angiocardiograms, and radiograms. The text is written in simple, clear, easily understood German script. Short differential diagnosis of the non-operable types of heart lesions are included. Line drawings show the pathophysiology of the conditions and the principles of the operative procedures. Only surgical principles are discussed and the details have been left for the surgeon to work out.

This is a good book for the practitioners, internists and surgeons who want a rapid survey of the field. The usual methods of study, history, and the physical examination, catheterization, and angiocardiography, with notes as to the value and limitations of each of the special diagnostic procedures, are touched upon. The indications and contraindications for surgery of congenital and acquired heart lesions are discussed. The definitive diagnostic procedures for the acquired lesion are not so well outlined as are those for the congenital ones.

Open heart surgery with the help of the extracorporeal circulation and the bypassing of the lungs, and the advantages and dangers of open heart surgery have not been dwelt upon. These new procedures are of relatively recent inception, within the year, and the current literature must be consulted and followed carefully for the advances of the present and the immediate future.

This monograph brings the subject up to the year 1958, and can be strongly recommended to those who wish to come abreast of the times in this field. The four pages of references are made up mostly from the European literature, but the important American contributions are cited. It is unfortunate that the authors did not record the statistics of their own experiences with each group of lesions, as the Scandinavians have done. The book is based on the personal expriences of the authors, and comprises 700 congenital, and over 500 acquired, angiocardiopathies.

The operations have been performed in each case after the question was asked and answered as to whether operative approach would completely or partially relieve the situation by the complete or partial re-establishment of the physiologic status which is the goal of every operation. Most cardiac surgeons admit that the operative cure and conspicuous improvement have been possible in only a small percentage of cardiac patients. The great majority of patients with heart disease, and even those who have been operated upon, need to be under the continuous care of a physician.

G. R. H.

Hypothermie et Chirurgie Cardiaque (Hypothermia and Cardiac Surgery). By Yannik Le Corroller, Paris, 1936, Librairie Maloine, 143 pages.

This thesis for the doctorate provides a convenient review of knowledge of this relatively new subject. The bibliography contains 75 references, well selected for their special significance. When this thesis was being written, the technique of extracorporeal circulation had not reached its present stage of development, and hypothermia was probably more important than it is now. However, even after the methods of extracorporeal circulation become more predictable and safer than they are now, there may remain certain circumstances under which hypothermia will be the method of choice for performing intracardiac surgery.

The author composed a practical treatise on the subject. Only 3 pages are devoted to its history, about 70 pages to physiology and pharmacology, about 15 pages to experimental cardiac surgery in animals, and 5 pages to cardiac surgery in human beings. A table which presents details about 16 cases in which Swan and his colleagues used hypothermia shows that the majority were cases in which pulmonic stenosis was corrected; a few cases of interauricular septal defect were also included.

In the last 40 pages of this small book, the author discusses the relation between hypothermia and the sympathetic nervous system, the state of artificial hibernation induced by drugs, and describes surgical experiments in which hypothermia was used.

H. S.

Announcements

A Course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. This is an advanced course intended only for experienced electrocardiographers. The class will meet daily from 9:00 A.M. to 5:00 P.M., Dec. 8 through 12, 1958.

Further information and a copy of the lecture schedule may be obtained from the secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

The Women's Medical Association of the City of New York offers the Mary Putnam Jacobi Fellowship to a graduate woman physician, either American or foreign. This Fellowship will start Oct. 1, 1959, and will amount to $2,000, $1,000 being available Oct. 1, 1959. The recipient of the Fellowship will be expected to make a report to the committee at the end of the fourth month, following which the second $1,000 will be awarded subject to the approval of the committee. The Fellowship is given for medical research, clinical investigation, or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the Fellowship but exception may be made by the committee under special circumstances.

Applications for this Fellowship may be obtained from the secretary of the committee after Aug. 1, 1958, and must be returned before Feb. 1, 1959, with the following information: (1) curriculum vitae, (2) a statement from a physician of a recent physical examination, (3) transcripts of college and medical school records, (4) personal letters of recommendation from two or more physicians under whom the applicant has studied, (5) a statement by the applicant of the problems she proposes to investigate or the study she plans to undertake, (6) a statement from the person under whom she proposes to study of his or her interest in the applicant's subject, and (7) recent photograph. All the above data must be at hand before the application will be considered.

Successful candidates will be notified not later than May 1, 1959.

Address: Ada Chree Reid, M.D., Secretary, 118 Riverside Drive, New York 24, N. Y.